# EXHIBIT 1

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## (54) ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

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Primary Examiner — Kimberly Chong (74) Attorney, Agent, or Firm — Sterne, Kessler, Goldstein & Fox P.L.L.C.

## (57) ABSTRACT

An antisense molecule capable of binding to a selected target site to induce exon skipping in the dystrophin gene, as set forth in SEQ ID NO: 1 to 214.

2 Claims, 22 Drawing Sheets

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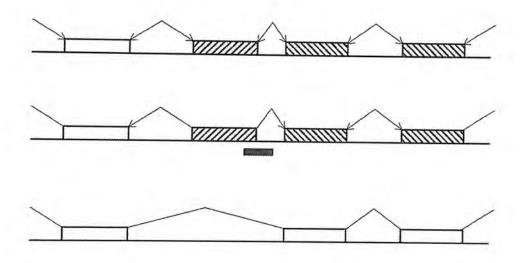


FIGURE 2

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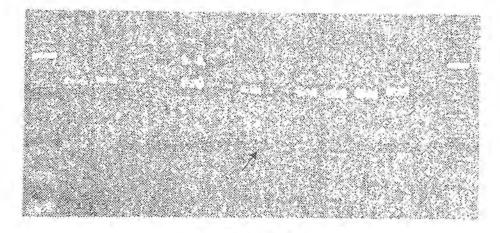


FIGURE 3

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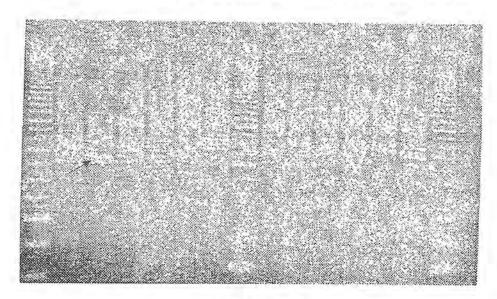


FIGURE 4

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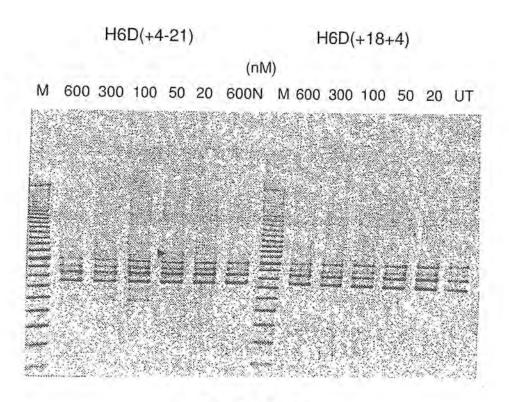


FIGURE 5

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6A(+69+91)



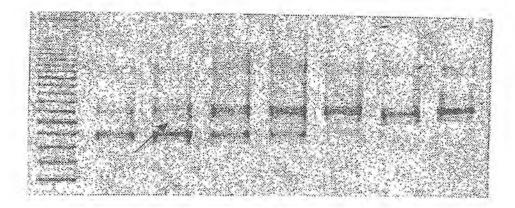


FIGURE 6

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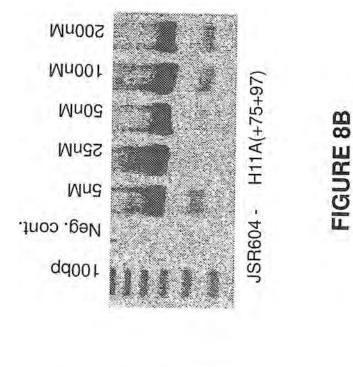
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FIGURE 7

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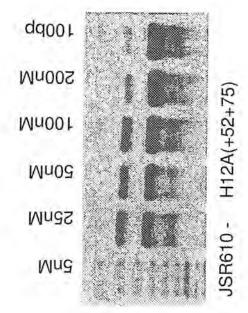
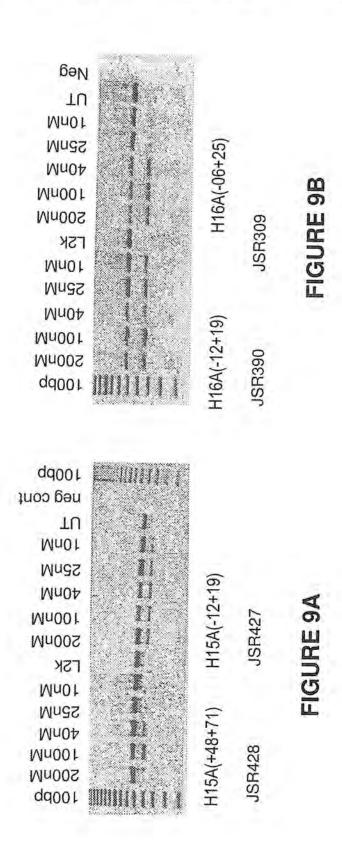


FIGURE 8A

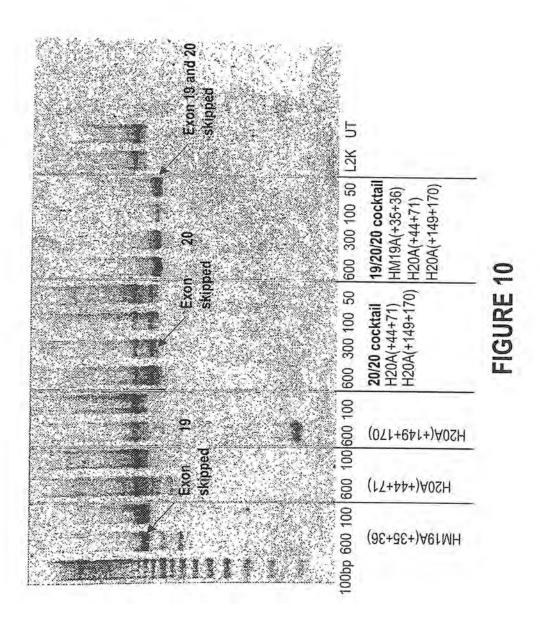
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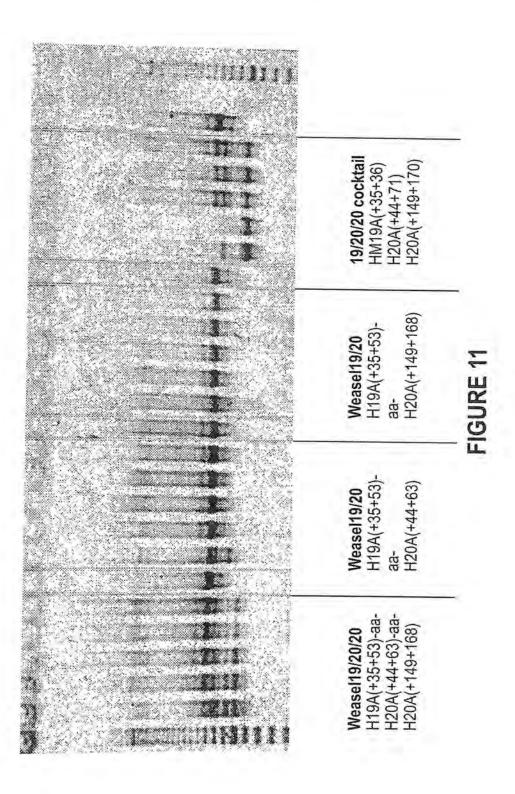
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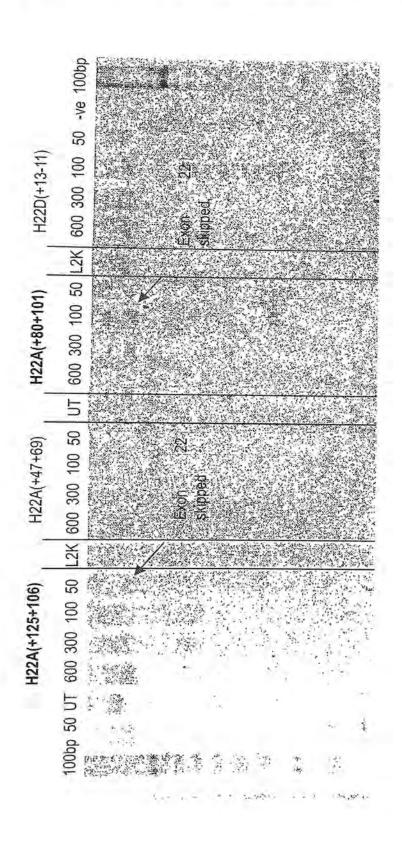


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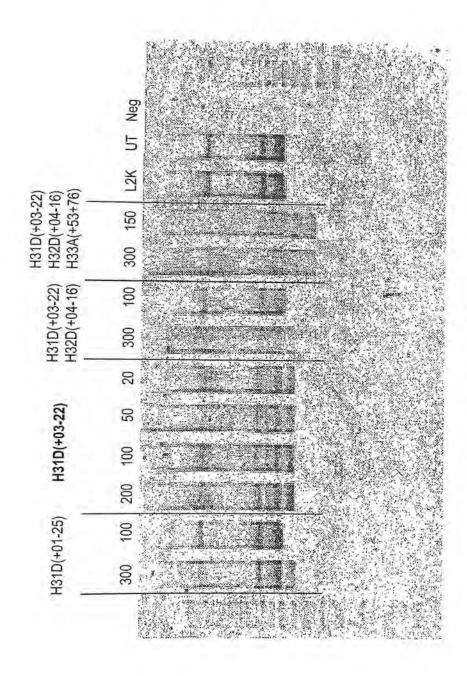
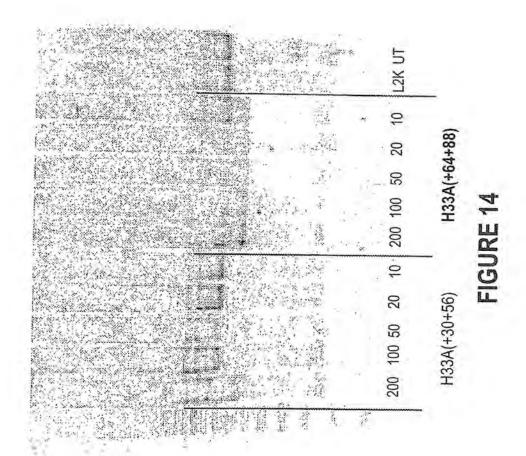
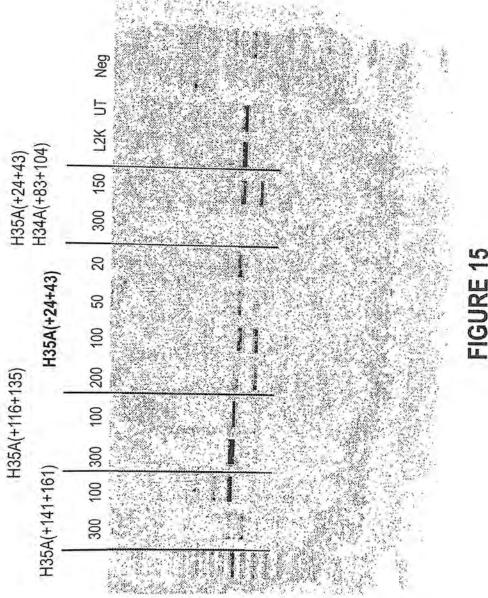


FIGURE 13

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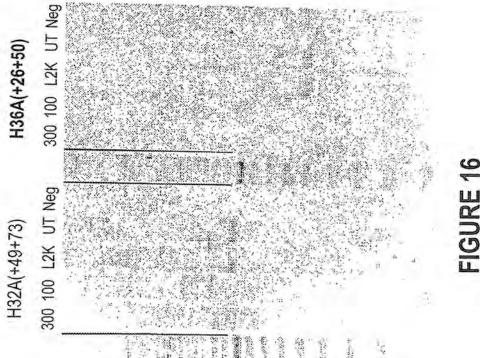


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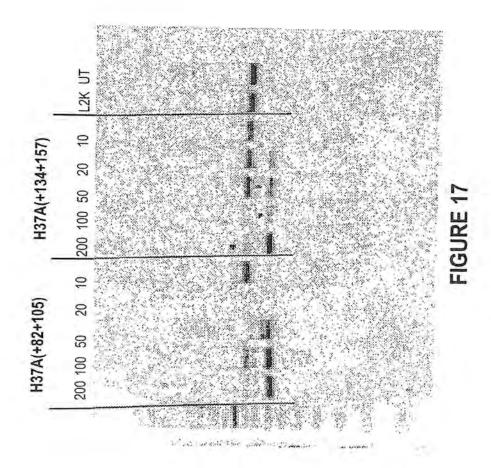
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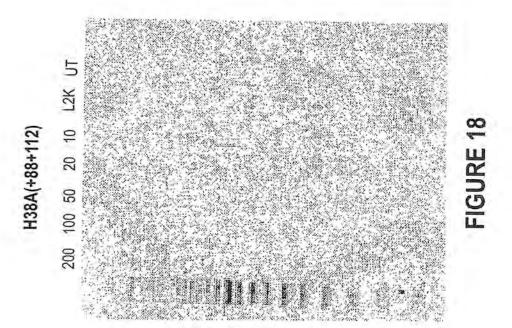
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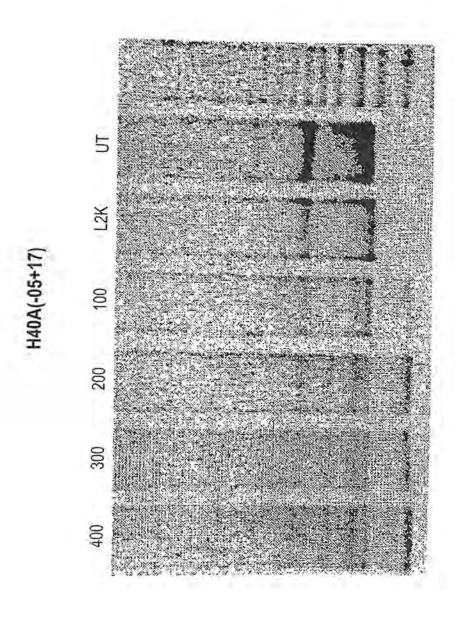
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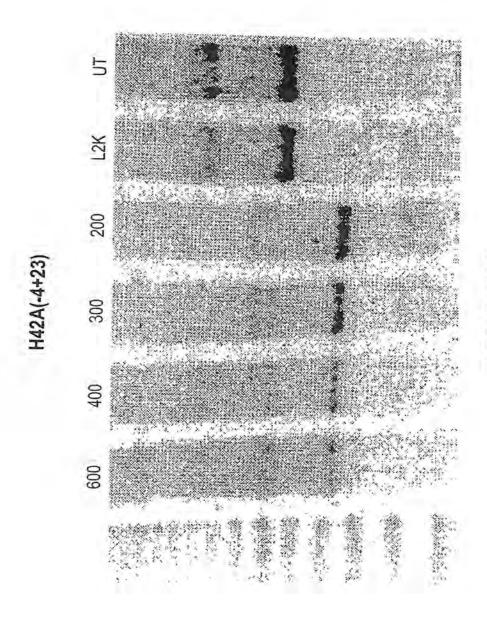


FIGURE 20

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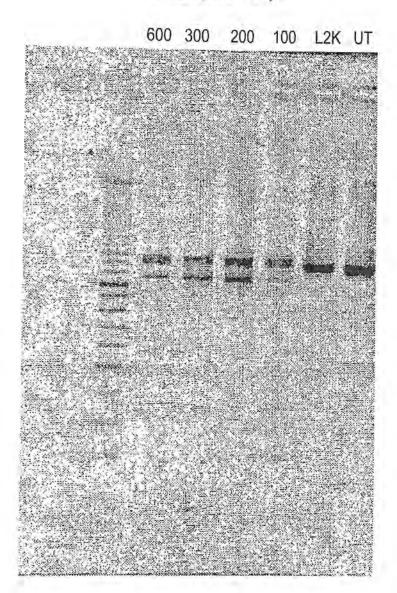


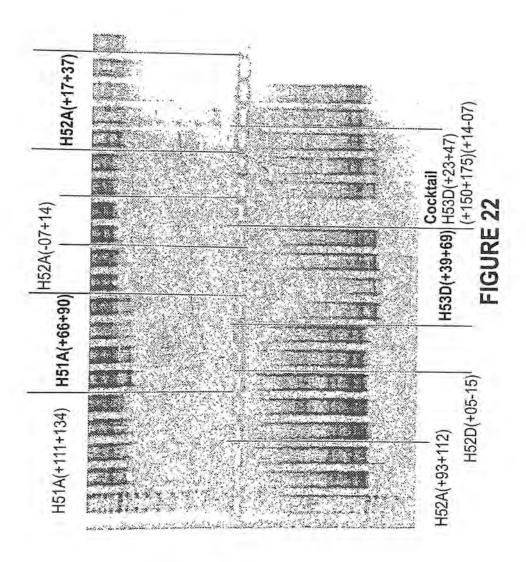
FIGURE 21

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### ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

# CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 15/274,772, filed Sep. 23, 2016, now pending, which application is a continuation of U.S. patent application Ser. No. 14/740,097, filed Jun. 15, 2015, now issued as U.S. Pat. No. 9,605,262, which application is a continuation of U.S. patent application Ser. No. 13/741,150, filed Jan. 14, 2013, now abandoned, which application is a continuation of U.S. patent application Ser. No. 13/168,857, filed Jun. 24, 15 2011, now abandoned, which application is a continuation of U.S. patent application Ser. No. 12/837,359, filed Jul. 15, 2010, now issued as U.S. Pat. No. 8,232,384, which application is a continuation of U.S. patent application Ser. No. 11/570,691, filed Jan. 15, 2008, now issued as U.S. Pat. No. 20 7,807,816, which application is a 35 U.S.C. § 371 National Phase Application of PCT/AU2005/000943, filed Jun. 28, 2005, which claims priority to Australian Patent Application No. 2004903474, filed Jun. 28, 2004; which applications are each incorporated herein by reference in their entireties.

#### STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with the application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is AVN-008CN41\_Sequence-Listing.txt. The text file is 62,086 Kilobytes, was created on Sep. 14, 2017 and is being submitted electronically via EFS-Web.

#### FIELD OF THE INVENTION

The present invention relates to novel antisense compounds and compositions suitable for facilitating exon skipping. It also provides methods for inducing exon skipping
using the novel antisense compounds as well as therapeutic
compositions adapted for use in the methods of the invention.

45

#### BACKGROUND ART

Significant effort is currently being expended researching methods for suppressing or compensating for disease-causing mutations in genes. Antisense technologies are being developed using a range of chemistries to affect gene expression at a variety of different levels (transcription, splicing, stability, translation). Much of that research has focused on the use of antisense compounds to correct or compensate for abnormal or disease-associated genes in a myriad of different conditions.

Antisense molecules are able to inhibit gene expression with exquisite specificity and because of this many research efforts concerning oligonucleotides as modulators of gene expression have focused on inhibiting the expression of targeted genes such as oncogenes or viral genes. The antisense oligonucleotides are directed either against RNA (sense strand) or against DNA where they form triplex structures inhibiting transcription by RNA polymerase II. To achieve a desired effect in specific gene down-regulation, the oligonucleotides must either promote the decay of the tar-

2

geted mRNA or block translation of that mRNA, thereby effectively preventing de novo synthesis of the undesirable target protein.

Such techniques are not useful where the object is to up-regulate production of the native protein or compensate for mutations which induce premature termination of translation such as nonsense or frame-shifting mutations. Furthermore, in cases where a normally functional protein is prematurely terminated because of mutations therein, a means for restoring some functional protein production through antisense technology has been shown to be possible through intervention during the splicing processes (Sierakowska H, et al., (1996) Proc Natl Acad Sci USA 93, 12840-12844; Wilton S D, et al., (1999) Neuromusc Disorders 9, 330-338; van Deutekom J C et al., (2001) Human Mol Genet 10, 1547-1554). In these cases, the defective gene transcript should not be subjected to targeted degradation so the antisense oligonucleotide chemistry should not promote target mRNA decay.

In a variety of genetic diseases, the effects of mutations on the eventual expression of a gene can be modulated through a process of targeted exon skipping during the splicing process. The splicing process is directed by complex multiparticle machinery that brings adjacent exon-intron junctions in pre-mRNA into close proximity and performs cleavage of phosphodiester bonds at the ends of the introns with their subsequent reformation between exons that are to be spliced together. This complex and highly precise process is mediated by sequence motifs in the pre-mRNA that are relatively short semi-conserved RNA segments to which bind the various nuclear splicing factors that are then involved in the splicing reactions. By changing the way the splicing machinery reads or recognises the motifs involved in pre-mRNA processing, it is possible to create differenthat the majority of human genes are alternatively spliced during normal gene expression, although the mechanisms invoked have not been identified. Using antisense oligonucleotides, it has been shown that errors and deficiencies in a coded mRNA could be bypassed or removed from the mature gene transcripts.

In nature, the extent of genetic deletion or exon skipping in the splicing process is not fully understood, although many instances have been documented to occur, generally at very low levels (Sherrat T G, et al., (1993) Am J Hum Genet 53, 1007-1015). However, it is recognised that if exons associated with disease-causing mutations can be specifically deleted from some genes, a shortened protein product can sometimes be produced that has similar biological properties of the native protein or has sufficient biological activity to ameliorate the disease caused by mutations associated with the target exon (Lu Q L, et al., (2003) Nature Medicine 9, 1009-1014; Aartsma-Rus A et al., (2004) Am J Hum Genet 74; 83-92).

This process of targeted exon skipping is likely to be particularly useful in long genes where there are many exons and introns, where there is redundancy in the genetic constitution of the exons or where a protein is able to function without one or more particular exons (e.g. with the dystrophin gene, which consists of 79 exons; or possibly some collagen genes which encode for repeated blocks of sequence or the huge nebulin or titin genes which are comprised of ~80 and over 370 exons, respectively).

Efforts to redirect gene processing for the treatment of genetic diseases associated with truncations caused by mutations in various genes have focused on the use of antisense oligonucleotides that either: (1) fully or partially overlap

with the elements involved in the splicing process; or (2) bind to the pre-mRNA at a position sufficiently close to the element to disrupt the binding and function of the splicing factors that would normally mediate a particular splicing reaction which occurs at that element (e.g., binds to the 5 pre-mRNA at a position within 3, 6, or 9 nucleotides of the element to be blocked).

For example, modulation of mutant dystrophin premRNA splicing with antisense oligoribonucleotides has been reported both in vitro and in vivo. In one type of 10 dystrophin mutation reported in Japan, a 52-base pair deletion mutation causes exon 19 to be removed with the flanking introns during the splicing process (Matsuo et al., (1991) J Clin Invest., 87:2127-2131). An in vitro minigene splicing system has been used to show that a 31-mer 15 2 -O-methyl oligoribonucleotide complementary to the 5 half of the deleted sequence in dystrophin Kobe exon 19 inhibited splicing of wild-type pre-mRNA (Takeshima et al. (1995), J. Clin. Invest., 95, 515-520). The same oligonucleotide was used to induce exon skipping from the native 20 dystrophin gene transcript in human cultured lymphoblastoid cells.

Dunckley et al., (1997) Nucleosides & Nucleotides, 16, 1665-1668 described in vitro constructs for analysis of splicing around exon 23 of mutated dystrophin in the mdx mouse mutant, a model for muscular dystrophy. Plans to 25 analyse these constructs in vitro using 2' modified oligonucleotides targeted to splice sites within and adjacent to mouse dystrophin exon 23 were discussed, though no target sites or sequences were given.

2'-O-methyl oligoribonucleotides were subsequently 30 reported to correct dystrophin deficiency in myoblasts from the mdx mouse from this group. An antisense oligonucleotide targeted to the 3' splice site of murine dystrophin intron 22 was reported to cause skipping of the mutant exon as well as several flanking exons and created a novel in-frame dystrophin transcript with a novel internal deletion. This mutated dystrophin was expressed in 1-2% of antisense treated mdx myotubes. Use of other oligonucleotide modifications such as 2'-O-methoxyethyl phosphodiesters are described (Dunckley et al. (1998) Human Mol. Genetics, 5, 1083-90).

Thus, antisense molecules may provide a tool in the treatment of genetic disorders such as Duchenne Muscular Dystrophy (DMD). However, attempts to induce exon skipping using antisense molecules have had mixed success. Studies on dystrophin exon 19, where successful skipping of that exon from the dystrophin pre-mRNA was achieved using a variety of antisense molecules directed at the flanking splice sites or motifs within the exon involved in exon definition as described by Errington et al. (2003) J Gen Med 5, 518-527"

In contrast to the apparent ease of exon 19 skipping, the 50 first report of exon 23 skipping in the mdx mouse by Dunckley et al., (1998) is now considered to be reporting only a naturally occurring revertant transcript or artefact rather than any true antisense activity. In addition to not consistently generating transcripts missing exon 23, Dunck- 55 ley et al., (1998) did not show any time course of induced exon skipping, or even titration of antisense oligonucleotides, to demonstrate dose dependent effects where the levels of exon skipping corresponded with increasing or decreasing amounts of antisense oligonucleotide. Furthermore, this work could not be replicated by other researchers.

The first example of specific and reproducible exon skipping in the mdx mouse model was reported by Wilton et al., (1999) Neuromuscular Disorders 9, 330-338. By directing an antisense molecule to the donor splice site, consistent and efficient exon 23 skipping was induced in the dystrophin 65 mRNA within 6 hours of treatment of the cultured cells. Wilton et al, (1999), also describe targeting the acceptor

region of the mouse dystrophin pre-mRNA with longer antisense oligonucleotides and being unable to repeat the published results of Dunckley et al., (1998). No exon skipping, either 23 alone or multiple removal of several flanking exons, could be reproducibly detected using a selection of antisense oligonucleotides directed at the acceptor splice site of intron 22.

While the first antisense oligonucleotide directed at the intron 23 donor splice site induced consistent exon skipping in primary cultured myoblasts, this compound was found to be much less efficient in immortalized cell cultures expressing higher levels of dystrophin. However, with refined targeting and antisense oligonucleotide design, the efficiency of specific exon removal was increased by almost an order of magnitude (see Mann C J et al., (2002) J Gen Med 4, 644-654).

Thus, there remains a need to provide antisense oligonucleotides capable of binding to and modifying the splicing of a target nucleotide sequence. Simply directing the antisense oligonucleotides to motifs presumed to be crucial for splicing is no guarantee of the efficacy of that compound in a therapeutic setting.

### SUMMARY OF THE INVENTION

The present invention provides antisense molecule compounds and compositions suitable for binding to RNA motifs involved in the splicing of pre-mRNA that are able to induce specific and efficient exon skipping and a method for their

The choice of target selection plays a crucial role in the efficiency of exon skipping and hence its subsequent application of a potential therapy. Simply designing antisense molecules to target regions of pre-mRNA presumed to be involved in splicing is no guarantee of inducing efficient and specific exon skipping. The most obvious or readily defined targets for splicing intervention are the donor and acceptor splice sites although there are less defined or conserved motifs including exonic splicing enhancers, silencing elements and branch points.

The acceptor and donor splice sites have consensus sequences of about 16 and 8 bases respectively (see FIG. 1 for schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing pro-

According to a first aspect, the invention provides antisense molecules capable of binding to a selected target to induce exon skipping.

For example, to induce exon skipping in exons 3 to 8, 10 to 16, 19 to 40, 42 to 44, 46, 47, and 50 to 53 in the Dystrophin gene transcript the antisense molecules are preferably selected from the group listed in Table 1A.

In a further example, it is possible to combine two or more antisense oligonucleotides of the present invention together to induce multiple exon skipping in exons 19-20, and 53. This is a similar concept to targeting of a single exon. A combination or "cocktail" of antisense oligonucleotides are directed at adjacent exons to induce efficient exon skipping.

In another example, to induce exon skipping in exons 19-20, 31, 34 and 53 it is possible to improve exon skipping of a single exon by joining together two or more antisense oligonucleotide molecules. This concept is termed by the inventor as a "weasel", an example of a cunningly designed antisense oligonucleotide. A similar concept has been described in Aartsma-Rus A et al., (2004) Am J Hum Genet 74: 83-92).

According to a second aspect, the present invention provides antisense molecules selected and or adapted to aid in the prophylactic or therapeutic treatment of a genetic disorder comprising at least an antisense molecule in a form suitable for delivery to a patient.

According to a third aspect, the invention provides a method for treating a patient suffering from a genetic disease wherein there is a mutation in a gene encoding a particular protein and the affect of the mutation can be abrogated by exon skipping, comprising the steps of: (a) selecting an antisense molecule in accordance with the methods described herein; and (b) administering the molecule to a patient in need of such treatment.

The invention also addresses the use of purified and isolated antisense oligonucleotides of the invention, for the manufacture of a medicament for treatment of a genetic 10

The invention further provides a method of treating a condition characterised by Duchenne muscular dystrophy, which method comprises administering to a patient in need of treatment an effective amount of an appropriately designed antisense oligonucleotide of the invention, relevant 15 to the particular genetic lesion in that patient. Further, the invention provides a method for prophylactically treating a patient to prevent or at least minimise Duchene muscular dystrophy, comprising the step of: administering to the patient an effective amount of an antisense oligonucleotide or a pharmaceutical composition comprising one or more of 20 these biological molecules.

The invention also provides kits for treating a genetic disease, which kits comprise at least a antisense oligonucleotide of the present invention, packaged in a suitable con-

tainer and instructions for its use.

Other aspects and advantages of the invention will become apparent to those skilled in the art from a review of the ensuing description, which proceeds with reference to the following figures.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 Schematic representation of motifs and domains involved in exon recognition, intron removal and the splic-

ing process (SEQ ID NOS: 213 and 214).

FIG. 2 Diagrammatic representation of the concept of 35 antisense oligonucleotide induced exon skipping to by-pass disease-causing mutations (not drawn to scale). The hatched box represents an exon carrying a mutation that prevents the translation of the rest of the mRNA into a protein. The solid black bar represents an antisense oligonucleotide that prevents inclusion of that exon in the mature mRNA

FIG. 3 Gel electrophoresis showing differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. The preferred compound [H8A(-06+18)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured normal human muscle cells. The less preferred antisense oligonucleotide [H8A(-06+14)] also induces efficient exon skipping, but at much higher concentrations. Other antisense oligonucleotides directed at exon 8 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

FIG. 4 Gel electrophoresis showing differing efficiencies of two antisense molecules directed at internal domains within exon 7, presumably exon splicing enhancers. The preferred compound [H7A(+45+67)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells. The less 55 preferred antisense oligonucleotide [H7A(+2+26)] induces only low levels of exon skipping at the higher transfection concentrations. Other antisense oligonucleotides directed at exon 7 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

FIG. 5 Gel electrophoresis showing an example of low 60 42. efficiency exon 6 skipping using two non-preferred antisense molecules directed at human exon 6 donor splice site. Levels of induced exon 6 skipping are either very low [H6D(+04-21)] or almost undetectable [H6D(+18-04)]. These are examples of non-preferred antisense oligonucleotides to 65

demonstrate that antisense oligonucleotide design plays a crucial role in the efficacy of these compounds.

FIG. 6 Gel electrophoresis showing strong and efficient human exon 6 skipping using an antisense molecules [H6A(+69+91)] directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle

FIG. 7 Gel electrophoresis showing strong human exon 4 skipping using an antisense molecule H4A(+13+32) directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells,

FIG. 8A Gel electrophoresis showing strong human exon 12 skipping using antisense molecule H12A(+52+75)

directed at exon 12 internal domain.

FIG. 8B Gel electrophoresis showing strong human exon 11 skipping using antisense molecule H11A(+75+97) directed at an exon 11 internal domain.

FIG. 9A Gel electrophoresis showing strong human exon 15 skipping using antisense molecules H15A(+48+71) and H15A(-12+19) directed at an exon 15 internal domain.

FIG. 9B Gel electrophoresis showing strong human exon 16 skipping using antisense molecules H16A(-12+19) and

H16A(-06+25).

FIG. 10 Gel electrophoresis showing human exon 19/20 skipping using antisense molecules H20A(+44+71) and H20A(+149+170) directed at an exon 20 and a "cocktail" of antisense oligonucleotides H19A(+35+65, H20A(+44+71) and H20A(+149+170) directed at exons 19/20.

FIG. 11 Gel electrophoresis showing human exon 19/20 skipping using "weasels" directed at exons 19 and 20.

FIG. 12 Gel electrophoresis showing exon 22 skipping using antisense molecules H22A(+125+106), H22A(+47+ 69), H22A(+80+101) and H22D(+13-11) directed at exon

FIG. 13 Gel electrophoresis showing exon 31 skipping using antisense molecules H31D(+01-25) and H31D(+03-22); and a "cocktail" of antisense molecules directed at exon

FIG. 14 Gel electrophoresis showing exon 33 skipping 40 using antisense molecules H33A(+30+56) and H33A(+64+ 88) directed at exon 33.

FIG. 15 Gel electrophoresis showing exon 35 skipping using antisense molecules H35A(+141+161), H35A(+116+ 135), and H35A(+24+43) and a "cocktail of two antisense molecules, directed at exon 35.

FIG. 16 Gel electrophoresis showing exon 36 skipping using antisense molecules H32A(+49+73) and H36A(+26+ 50) directed at exon 36.

FIG. 17 Gel electrophoresis showing exon 37 skipping using antisense molecules H37A(+82+105) and H37A(+ 134+157) directed at exon 37.

FIG. 18 Gel electrophoresis showing exon 38 skipping using antisense molecule H38A(+88+112) directed at exon

FIG. 19 Gel electrophoresis showing exon 40 skipping using antisense molecule H40A(-05+17) directed at exon

FIG. 20 Gel electrophoresis showing exon 42 skipping using antisense molecule H42A(-04+23) directed at exon

FIG. 21 Gel electrophoresis showing exon 46 skipping using antisense molecule H46A(+86+115) directed a# exon

FIG. 22 Gel electrophoresis showing exon 51, exon 52 and exon 53 skipping using various antisense molecules directed at exons 51, 52 and 53, respectively. A "cocktail" of antisense molecules is also shown directed at exon 53.

### 7 BRIEF DESCRIPTION OF THE SEQUENCE LISTINGS

### TABLE 1A

Description of 2'-0-methyl phosphorothicate antisense oligonuclectides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-0-methyl antisense oligonuclectides are more RNA- like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ<br>ID SEQUENCE | NUCLEOTIDE SEQUENCE (5'-3')                  |
|--------------------|--|
| 1 H8A(-06+18)      | GAU AGG UGG UAU CAA CAU CUG UAA              |
| 2 H8A (-03+18)     | GAU AGG UGG UAU CAA CAU CUG                  |
| 3 H8A(-07+18)      | GAU AGG UGG UAU CAA CAU CUG UAA G            |
| 4 H8A(-06+14)      | GGU GGU AUC AAC AUC UGU AA                   |
| 5 H8A(-10+10)      | GUA UCA ACA UCU GUA AGC AC                   |
| 6 H7A(+45+67)      | UGC AUG UUC CAG UCG UUG UGU GG               |
| 7 H7A(+02+26)      | CAC UAU UCC AGU CAA AUA GGU CUG G            |
| 8 H7D(+15-10)      | AUU UAC CAA CCU UCA GGA UCG AGU A            |
| 9 H7A(-18+03)      | GGC CUA AAA CAC AUA CAC AUA                  |
| 10 C6A(-10+10)     | CAU UUU UGA CCU ACA UGU GG                   |
| 11 C6A (-14+06)    | UUU GAC CUA CAU GUG GAA AG                   |
| 12 C6A(-14+12)     | UAC AUU UUU GAC CUA CAU GUG GAA AG           |
| 13 C6A(-13+09)     | AUU UUU GAC CUA CAU GGG AAA G                |
| 14 CH6A(+69+91)    | UAC GAG UUG AUU GUC GGA CCC AG               |
| 15 C6D(+12-13)     | GUG GUC UCC UUA CCU AUG ACU GUG G            |
| 16 C6D(+06-11)     | GGU CUC CUU ACC UAU GA                       |
| 17 H6D(+04-21)     | UGU CUC AGU AAU CUU CUU ACC UAU              |
| 18 H6D(+18-04)     | UCU UAC CUA UGA CUA UGG AUG AGA              |
| 19 H4A(+13+32)     | GCA UGA ACU CUU GUG GAU CC                   |
| 20 H4D(+04-16)     | CCA GGG DAC DAC DUA CAU DA                   |
| 21 H4D(-24-44)     | AUC GUG UGU CAC AGC AUC CAG                  |
| 22 H4A(+11+40)     | UGU UCA GGG CAU GAA CUC UUG UGG AUC          |
| 23 H3A(+30+60)     | UAG GAG GCG CCU CCC AUC CUG UAG GUC<br>ACU G |
| 24 H3A(+35+65)     | AGG UCU AGG AGG CGC CUC CCA UCC UGU<br>AGG U |
| 25 H3A(+30+54)     | GCG CCU CCC AUC CUG UAG GUC ACU G            |
| 26 H3D(+46-21)     | CUU CGA GGA GGU CUA GGA GGC GCC UC           |
| 27 H3A (+30+50)    | CUC CCA UCC UGU AGG UCA CUG                  |
|                    | UAC CAG UUU UUG CCC UGU CAG G                |
|                    | UCA AUA UGC UGC UUC CCA AAC UGA AA           |
|                    | CUA GGA GGC GCC UCC CAU CCU GUA G            |

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# TABLE 1A-continued

Description of 2'-O-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA- like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ<br>ID SEQUENCE | NUCLEOTIDE SEQUENCE (5'-3')            |
|--------------------|--|
| 31 H5A(+20+50)     | UUA UGA UUU CCA UCU ACG AUG UCA GUA    |
| 32 H5D(+25-05)     | CUU ACC UGC CAG UGG AGG AUU AUA UUC    |
| 33 H5D (+10-15)    | CAU CAG GAU UCU UAC CUG CCA GUG G      |
| 34 H5A(+10+34)     | CGA UGU CAG UAC UUC CAA UAU UCA C      |
| 35 H5D(-04-21)     | ACC AUU CAU CAG GAU UCU                |
| 36 HSD(+16-02)     | ACC UGC CAG UGG AGG AUU                |
| 37 H5A(-07+20)     | CCA AUA UUC ACU AAA UCA ACC UGU UAA    |
| 38 H5D(+18-12)     | CAG GAU UGU UAC CUG CCA GUG GAG GAU    |
| 39 H5A (+05+35)    | ACG AUG UCA GUA CUU CCA AUA UUC ACU    |
| 40 H5A(+15+45)     | AUU UCC AUC UAC GAU GUC AGU ACU UCC    |
| 41 H10A(-05+16)    | CAG GAG CUU CCA AAU GCU GCA            |
| 42 H10A(-05+24)    | CUU GUC UUC AGG AGC UUC CAA AUG CUG CA |
| 43 H10A(+98+119)   | UCC UCA GCA GAA AGA AGC CAC G          |
| 44 HlOA(+130+149)  | UUA GAA AUC UCU CCU UGU GC             |
| 45 H10A(-33-14)    | UAA AUU GGG UGU UAC ACA AU             |
| 46 H11D(+26+49)    | CCC UGA GGC AUU CCC AUC UUG AAU        |
| 47 H11D(+11-09)    | AGG ACU UAC UUG CUU UGU UU             |
| 48 H11A(+118+140)  | CUU GAA UUU AGG AGA UUC AUC UG         |
| 49 H11A(+75+97)    | CAU CUU CUG AUA AUU UUC CUG UU         |
| 50 H12A(+52+75)    | UCU UCU GUU UUU GUU AGC CAG UCA        |
| 51 H12A(-10+10)    | UCU AUG UAA ACU GAA AAU UU             |
| 52 H12A(+11+30)    | UUC UGG AGA UCC AUU AAA AC             |
| 53 H13A(+77+100)   | CAG CAG UUG CGU GAU CUC CAC UAG        |
| 54 H13A(+55+75)    | UUC AUC AAC UAC CAC CAC CAU            |
| 55 H13D(+06-19)    | CUA AGC AAA AUA AUC UGA CCU UAA G      |
| 56 H14A(+37+64)    | CUU GUA AAA GAA CCC AGC GGU CUU CUG U  |
|                    | CAU CUA CAG AUG UUU GCC CAU C          |
|                    | GAA GGA UGU CUU GUA AAA GAA CC         |
|                    | ACC UGU UCU UCA GUA AGA CG             |
|                    | CAU GAC ACA CCU GUU CUU CAG UAA        |
|                    | CAU UUG AGA AGG AUG UCU UG             |
|                    | AUC UCC CAA UAC CUG GAG AAG AGA        |
|                    |  |

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# TABLE 1A-continued

Description of 2'-O-methyl phosphorothicate antisense oligonuclectides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonuclectides are more RNA- like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ  | SEQUENCE       | NUCLEOTIDE SEQUENCE (5'-3')                  |
|------|----------------|--|
| 63   | H15A(-12+19)   | GCC AUG CAC UAA AAA GGC ACU GCA AGA          |
| 64   | H15A(+48+71)   | UCU UUA AAG CCA GUU GUG UGA AUC              |
| 65   | H15A(+08+28)   | UUU CUG AAA GCC AUG CAC UAA                  |
| 66   | H15D(+17-08)   | GUA CAU ACG GCC AGU UUU UGA AGA C            |
| 67   | H16A(-12+19)   | CUA GAU CCG CUU UUA AAA CCU GUU AAA          |
| 68   | H16A(-06+25)   | UCU UUU CUA GAU CCG CUU UUA AAA CCU          |
| 69   | H16A(-06+19)   | CUA GAU CCG CUU UUA AAA CCU GUU A            |
| 70   | H16A(+87+109)  | CCG UCU UCU GGG UCA CUG ACU UA               |
| 71   | H16A(-07+19)   | CUA GAU CCG CUU UUA AAA CCU GUU AA           |
| 72 1 | H16A(-07+13)   | CCG CUU UUA AAA CCU GUU AA                   |
| 73 I | H16A(+12+37)   | UGG ADU GCU DUU UCU DUU CUA GAU CC           |
| 74 F | H16A(+92+116)  | CAU GCU UCC GUC UUC UGG GUC ACU G            |
| 75 F | H16A(+45+67)   | G AUC UUG UUU GAG UGA AUA CAG U              |
| 76 F | (16A(+105+126) | GUU AUC CAG CCA UGC UUC CGU C                |
| 77 H | N16D(+05-20)   | UGA UAA UUG GUA UCA CUA ACC UGU G            |
| 78 H | M16D(+12-11)   | GUA UCA CUA ACC UGU GCU GUA C                |
| 79 H | 119A(+35+53)   | CUG CUG GCA UCU UGC AGU U                    |
| 30 н | 19A(+35+65)    | GCC UGA GCU GAU CUG CUG GCA UCU UGC<br>AGU U |
| 31 H | 20A(+44+71)    | CUG GCA GAA UUC GAU CCA CCG GCU GUU C        |
| 32 H | 20A(+147+168)  | CAG CAG UAG UUG UCA UCU GCU C                |
| з н  | 20A(+185+203)  | UGA UGG GGU GGU GGG UUG G                    |
| 4 H  | 20A(-0B+17)    | AUC UGC AUU AAC ACC CUC UAG AAA G            |
| 5 H: | 20A(+30+53)    | CCG GCU GUU CAG UUG UUC UGA GGC              |
| 6 H  | 20A(-11+17)    | AUC UGC AUU AAC ACC CUC UAG AAA GAA A        |
| 7 H2 | 20D(+08-20)    | GAA GGA GAA GAG AUU CUU ACC UUA CAA A        |
| 8 H2 | OA(+44+63)     | AUU CGA UCC ACC GGC UGU UC                   |
| 9 H2 | OA(+149+168    | CAG CAG UAG UUG UCA UCU GC                   |
|      |                | GCC GGU UGA CUU CAU CCU GUG C                |
|      |                | CUG CAU CCA GGA ACA UGG GUC C                |
|      |                | GUC UGC AUC CAG GAA CAU GGG UC               |
|      |                | GUU GAA GAU CUG AUA GCC GGU UGA              |
|      |                | UAC UUA CUG UCU GUA GCU CUU UCU              |
|      |                | CAC UCA UGG UCU CCU GAU AGC GCA              |

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## TABLE 1A-continued

Description of 2'-O-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA: Since these 2'-O-methyl antisense oligonucleotides are more RNA- like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| 96 H22A(+125+106) 97 H22A(+47+69) ACU GCU GGA CCC AUG UCU CUGA UG 98 H22A(+80+101) CUA AGU UGA GGU AUG GAG AGU 99 H22D(+13-11) UAU UCA CAG ACC UGC AAU UCC CC 100 H23A(+34+59) ACA GUG GUG CUG AGA UAG UAU AGG CCC 101 H23A(+18+39) UAG GCC ACU UUG UUG CU UUG C 102 H23A(+72+90) UUC AGA GGG CGC UUU CUU CU 103 H24A(+08+70) GGG CAG GCC AUU CCU UCA GA 104 H24A(-02+22) UCU UCA GGG UUU GUA UGU AUG UUCU 105 H25A(+131+156) CUG UUG GCC UGA AUU UGA CCA CUG AG 107 H25D(+16-08) GUC UAU ACC UGU UGG CAC AUG UGA AUA UCC CCA 108 H26A(+132+156) UGC UUU CUG UUG UGG CAC AUG UGG AGU UCC 110 H26A(+68+92) UGU GCC CCU UUU GUG CAA AGU CCU CCU UCA GA 111 H27A(+82+106) UUA AGG CCU CUU UUG CGC AUC UCU GA 112 H27A(-4+19) GGG GCC UCU CUU UAG CCC UCU GA 113 H27D(+19-03) GAC UUC CAA AGU CUU GCU UCU AAG 114 H28A(-05+19) GCC AAC AUG CCC AAA CUU CCU AAG 115 H28A(+99+124) CAG AGA UUU CCU CAG ACC UCA GAG 117 H29A(+57+81) UCC GCC AUC UGU UAG GGU CCC CCC CCC 119 H29D(+17-05) CAU ACC UCU UCA AGU CCC UCU GUC CCC 120 H30A(+22+147) CAU UUG AGC CUC CCU GAG GCC UCU UCU 121 H30A(+25+50) UCC UGG GCA GAC UCC CCC GAG GAC 122 H30D(+19-04) UUC UGA AAU AAC AUA UAC CUG UGC 123 H31D(+06-18) UUC UGA AAU CAA UAC AUA UAC CUG UGC 124 H31D(+03-22) UAG UUC UGA AAU CAA UAU ACC UCU GA 125 H31A(+05+25) GAC UUC UCA AAU CAA AUA ACC UCU UGU 127 H32D(+04-16) CAC CAG AAA UAC AUA CAC CAC 127 H32D(+04-16) | SEQ<br>ID SEQUENCE | NUCLEOTIDE SEQUENCE (5'-3')        |
|--|--------------------|------------------------------------|
| 97 H22A(+47+69) 98 H22A(+80+101) CUA AGU UGA GGU AUG GAG AGU 99 H22D(+13-11) UAU UCA CAG ACC UGC AAU UCC CC 100 H23A(+34+59) ACA GUG GUG CUG AGA UAG UAU AGG CC 101 H23A(+18+39) UAG GCC ACU UUG DUG CUC UUG C 102 H23A(+72+90) UUC AGA GGG CGC DUU CUU C 103 H24A(+48+70) GGG CAG GCC AUU CCU CCU UCA GA 104 H24A(-02+22) UCU UCA GGG UUU GUA UCU UCU 105 H25A(+9+36) CUG GGC UGA AUU GUC UGA AUA UCA CUC 106 H25A(+131+156) CUG UUG GCA CAU GUG AUC CCA CUG AG 107 H25D(+16-08) GUC UAU ACC UGU UGG CAC AUG UGA 108 H26A(-07+19) CCU CCU UUC UGG CAU AGA CCU UCC AC 110 H26A(+68+92) UGU GUC AUC CAU UCG UGA AUC UCU GG 111 H27A(+82+106) UUA AGG CCU CUU UGG CA CAU GUG AG 112 H27A(-4+19) GGG GCU CUU CUU UAG CUC UCU GA 113 H27D(+19-03) GAC UUC CAA AGU CUU GCA AUU CCU AAG 114 H28A(-05+19) GCC AAC AUG CCC AAA CUU CCU AAG 115 H28A(+99+124) CAG AGA UUU CCU CAG GGC UCA GAG 117 H29A(+57+81) UCC GCC AUC UUU AGG GGU CUG UGC C 118 H29A(+18+42) AUU UGG GCA AUC UCU UGA GGU CUG UCC C 119 H29D(+17-05) CAU ACC UCU UAA GGC CUC GAG GAU 110 H29A(+25+50) UCC UGG GCA GAC UCC GAG GAC UCC 124 H31D(+04-20) UAG CUC GAA AUA CAU AUA CCU GG 125 H31A(+05+25) GAC UUG UCA AAU ACC AUA CCU CGG 127 H32D(+04-16) CAC CAG AAA AUA CAU AUA CCA CA  | 96 H22A(+125+106)  | CUG CAA UUC CCC GAG UCU CUG C      |
| 98 H22A(+80+101) CUA AGU UGA GGU AUG GAG AGU  99 H22D(+13-11) UAU UCA CAG ACC UGC AAU UCC CC  100 H23A(+34+59) ACA GUG GUG CUG AGA UAG UAU AGG CC  101 H23A(+18+39) UAG GCC ACU UUG UUG CC UUG CC  102 H23A(+72+90) UUC AGA GGG CGC UUU CUU CC  103 H24A(+48+70) GGG CAG GCC AUU CCU CCU UCA GA  104 H24A(-02+22) UCU UCA GGG UUU GUU GUU CC  105 H25A(+9+36) CUG GGC UAA AUU GUC UGA AUA UCA CUC  106 H25A(+131+156) CUG UUG GCA CAU GUG AUC CCA CUG AG  107 H25D(+16-08) GUC UAU ACC UGU UGG CAC AUG UGA  108 H26A(+132+156) UGC UUU CUG UAA UUC AUC UGG AGU U  110 H26A(+68+92) UGU GUC AUC CAU UCG UGC ACC  111 H27A(+82+106) UUA AGG CCU CUU UAG CUC UCC GC  112 H27A(-4+19) GGG GCU CUU CUU UAG CUC UCU GA  113 H27D(+19-03) GAC UUC CAA AGU CUU GCA UUU C  114 H28A(-05+19) GCC AAC AUG CCC AAA CUU CCU AAG  115 H28A(+99+124) CAG AGA UUU CCU CAG CUC CGC CAG GA  116 H28D(+16-05) CUU ACA UCU AGC CUC UGA AGG  117 H29A(+57+81) UCC GCC AUC UGU UAG GGU CUG UGC C  120 H30A(+22+147) CAU UUG AGC UCC UGA AGU UCC C  121 H30A(+25+50) UCC UGG GCA GAC CUC UGG UCC UCC UGU UCC UGG CAG GAC UCC UCG UCC UCC UCC UCC UCC UCC UCC UC   |                    |                                    |
| 100 H23A(+34+59) 101 H23A(+18+39) 102 H23A(+18+39) 103 H24A(+48+70) 104 H24A(-02+22) 105 H25A(+31+156) 106 H25A(+31+156) 107 H25A(+31+156) 108 H26A(+132+156) 109 H26A(-07+19) 109 H26A(-07+19) 100 H26A(+68+92) 110 H27A(-44+19) 111 H27A(-48+106) 112 H27A(-41+19) 113 H27D(+19-03) 114 H28A(+05+124) 115 H28A(+95+160) 116 H25A(+95+160) 117 H25B(+16-05) 118 H26A(+16-05) 119 H26A(+16-05) 110 H26A(+16-05) 111 H27A(+16-05) 112 H27A(+16-05) 113 H27B(+16-05) 114 H28A(+05+19) 115 H28A(+16-05) 116 H28A(+16-05) 117 H29A(+57+81) 118 H29A(+18+42) 119 H20B(+17-05) 120 H30A(+122+147) 121 H30A(+22+147) 122 H30D(+19-04) 123 H31D(+06-18) 124 H31D(+06-18) 125 H31A(+05+25) 126 H31D(+06-16) 127 H32D(+04-16) 127 H32D(+04-16) 127 H32D(+04-16) 120 GCC CAG GAA CAG CAG CAG CAG CAG CAG CAG  | 98 H22A(+80+101)   |                                    |
| 100 H23A(+34+59) 101 H23A(+18+39) 102 H23A(+72+90) 103 H24A(+48+70) 105 GC ACU UUG UUG CU UUG C 104 H24A(-02+22) 105 H25A(+9+36) 106 H25A(+9+36) 107 H25D(+16-08) 108 H26A(+132+156) 109 H26A(-07+19) 109 H26A(-07+19) 110 H27A(+8+106) 111 H27A(+8+106) 112 H27A(-4+19) 113 H27D(+19-03) 114 H28A(+99+124) 115 H28A(+99+124) 116 H29A(+18-78) 117 H29A(+18-78) 118 H29A(+18-78) 119 H29D(+17-05) 120 H30A(+122+147) 121 H30A(+22+147) 122 H30D(+19-04) 123 H31D(+06-18) 124 H31D(+03-22) 125 H31A(+05+25) 126 GC UG UUG GA AUG CA AUG UGG 127 H32D(+04-16) 127 H32D(+04-16) 127 H32D(+04-16) 127 H32D(+04-16) 128 H31A(+05+25) 120 GC GC AUG UCG GA AUG UCG GA 120 UCG GG GCU CUU CUU GG GCA AUG UCG UCG CUGG GGG GCU GCG GGG GCG GCG   | 99 H22D(+13-11)    |                                    |
| 101 H23A(+18+39) UAG GCC ACU UUG UUG CU UUG C 102 H23A(+72+90) UUC AGA GGG CGC UUU CUU C 103 H24A(+48+70) GGG CAG GCC AUU CCU CCU UCA GA 104 H24A(-02+22) UCU UCA GGG UUU GUA UGU GAU UCU 105 H25A(+9+36) CUG GGC UGA AUU GUC UGA AUA UCA CUG 106 H25A(+131+156) CUG UUG GCA CAU GUG AUC CCA CUG AG 107 H25D(+16-08) GUC UAU ACC UGU UGG CAC AUG UGA 108 H26A(+032+156) UGC UUU CUG UAA UUC AUC UGG AGU U 109 H26A(-07+19) CCU CCU UUC UGG CAU AGA CCU UCC AC 110 H26A(+68+92) UGU GUC AUC CAU UCG UGA CAU GUG GG 111 H27A(+82+106) UUA AGG CCU CUU GUG CUA CAG GUG G 112 H27A(-4+19) GGG GCU CUU CUU UAG CUC UCU GA 113 H27D(+19-03) GAC UUC CAA AGU CUU GCA UUU C 114 H28A(-05+19) GCC AAC AUG CCC AAA CUU CCU AAG 115 H28A(+99+124) CAG AGA UUU CCU CAG CUC CGC CAG GA 116 H29D(+16-05) CUU ACA UCU AGG ACC UCA GAG 117 H29A(+57+81) UCC GCC AUC UGU UAG GGU CUG UGC C 119 H29D(+17-05) CAU ACC UCU UCA UGU AGU UCC C 120 H30A(+122+147) CAU UUG AGC UCC UGA AUG UCC C 121 H30A(+25+50) UCC UGG GCA GAC UGG AUG UCC UGU UCC 122 H30D(+19-04) UUG CUG AAA UAA CAU AUA CCU G 123 H31D(+06-18) UUC UGA AAU AAC AUA UAC CUG UGA 124 H31D(+03-22) UAG UUC CUA AAU CAG AUU GGA 125 H31A(+05+25) GAC UUG GAA AUA ACA UAU ACC UGU 127 H32D(+04-16) CAC CAG AAA UAC CUA CAC  | 100 H23A(+34+59)   |                                    |
| 102 H23A(+72+90) 103 H24A(+48+70) 104 H24A(-02+22) 105 H25A(+9+36) 106 H25A(+131+156) 107 H25D(+16-08) 108 H26A(+132+156) 109 H26A(-07+19) 109 H26A(-07+19) 110 H27A(-48+92) 111 H27A(+82+106) 112 H27A(-4+19) 113 H27D(+19-03) 114 H28A(-05+19) 115 H28A(+95+124) 116 H29A(+57+81) 117 H29A(+57+81) 118 H29A(+152+147) 119 H29D(+17-05) 120 H30A(+22+147) 121 H30A(+22+147) 122 H30D(+19-04) 123 H31D(+06-18) 124 H31D(+03-22) 124 H31D(+04-20) 126 H31D(+04-16) 120 UUU AGA GGC CUU CUU CUU CUU CUU CUU CUU CUU CUU  | 101 H23A(+18+39)   |                                    |
| 103 H24A(+48+70) GGG CAG GCC AUU CCU CCU UCA GA 104 H24A(-02+22) UCU UCA GGG UUU GUA UGU GAU UCU 105 H25A(+9+36) CUG GGC UGA AUU GUC UGA AUA UCA CUC 106 H25A(+131+156) CUG UUG GCA CAU GUG AUC CCA CUG AG 107 H25D(+16-08) GUC UAU ACC UGU UGG CAC AUG UGA 108 H26A(+132+156) UGC UUU CUG UAA UUC AUC UGG AGU U 109 H26A(-07+19) CCU CCU UUC UGG CAU AGA CCU UCC AC 110 H26A(+68+92) UGU GUC AUC CAU UCG UGC AUC UCU G 111 H27A(+82+106) UUA AGG CCU CUU GUG CUA CAG GUG G 112 H27A(-4+19) GGG GCU CUU CUU UAG CUC UCU GA 113 H27D(+19-03) GAC UUC CAA AGU CUU GCA UUU C 114 H28A(+99+124) CAG AGA UUU CCU CAG CUC CGC CAG GA 115 H28A(+99+124) CAG AGA UUU CCU CAG GUC GC CAG GA 116 H28D(+16-05) CUU ACA UCU AGC ACC UCA GAG 117 H29A(+57+81) UCC GCC AUC UGU UAA GGU CUC UG CC 118 H29A(+18+42) AUU UGG GUU AUC CUC UGA AUG UCC C 119 H29D(+17-05) CAU ACC UCU UCA UGU AGG UCC C 120 H30A(+122+147) CAU UUG AGC UGC GAC CUU GUC UG 121 H30A(+25+50) UCC UGG GCA GAC UGG AUG CUC UGU UC 122 H30D(+19-04) UUG CCU GGG CUU CCU GAG GCA 124 H31D(+06-18) UUC UGA AAU AAC AUA UAC CUG UGC 125 H31A(+05+25) GAC UUG UCA AAU CAU AUA CCU GU 126 H31D(+04-20) GUU UCU GAA AUA ACA UAU ACC UGU 127 H32D(+04-16) CAC CAG AAA UAC AUA CCA CA  | 102 H23A(+72+90)   |                                    |
| 104 H24A(-02+22) 105 H25A(+9+36) CUG GGC UGA AUU GUC UGA AUA UCA CUG 106 H25A(+131+156) CUG UUG GCA CAU GUG AUC CCA CUG AG 107 H25D(+16-08) GUC UAU ACC UGU UGG CAC AUG UGA 108 H26A(+132+156) UGC UUU CUG UAA UUC AUC UGG AGU U 109 H26A(-07+19) CCU CCU UUC UGG CAU AGA CCU UCC AC 110 H26A(+68+92) UGU GUC AUC CAU UCG UGA AUC UCU GA 111 H27A(+82+106) UUA AGG CCU CUU UUG CUG CAU CAG GUG G 112 H27A(-4+19) GGG GCU CUU CUU UAG CUC UCU GA 113 H27D(+19-03) GAC UUC CAA AGU CUU GCA UUU C 114 H28A(+99+124) CAG AGA UUU CCU CAG CUC CGC CAG GA 116 H28D(+16-05) CUU ACA UCU AGC ACC UCA GAG 117 H29A(+57+81) UCC GCC AUC UGU UAG GGU CUG UGC C 118 H29A(+18+42) AUU UGG GUU AUC CUC UGA AUG UCC C 120 H30A(+122+147) CAU UUG AGC UCC UGA GAG CUC UGU UG 121 H30A(+25+50) UCC UGG GCA GAC UCG GAG GCA UU 122 H30D(+19-04) UUG CUG AAA UAA CAU AUA CCU GGA 124 H31D(+06-18) UUC UGA AAU CAC AUA CAG AUU GCU 125 H31A(+05+25) GAC UUG UCA GAA AUA CAG AUU GGA 126 H31D(+04-20) CAC CAG AAA UAC AUA CAG AUU ACC UGU 127 H32D(+04-16) CAC CAG AAA UAC AUA CAG AUU CCU GGA 127 H32D(+04-16) CAC CAG AAA UAC AUA CCA CA  | 103 H24A(+48+70)   |                                    |
| CUG GGC UGA AUU GUC UGA AUA UCA CUC  106 H25A(+131+156) CUG UUG GCA CAU GUG AUC CCA CUG AG  107 H25D(+16-08) GUC UAU ACC UGU UGG CAC AUG UGA  108 H26A(+132+156) UGC UUU CUG UAA UUC AUC UGG AGU U  109 H26A(-07+19) CCU CCU UUC UGG CAU AGA CCU UCC AC  110 H26A(+68+92) UGU GUC AUC CAU UCG UGC AUC UCU G  111 H27A(+82+106) UUA AGG CCU CUU GUG CUA CAG GUG G  112 H27A(-4+19) GGG GCU CUU CUU UAG CUC UCU GA  113 H27D(+19-03) GAC UUC CAA AGU CUU GCA UUU C  114 H28A(-05+19) GCC AAC AUG CCC AAA CUU CCU AAG  115 H28A(+99+124) CAG AGA UUU CCU CAG CUC CGC CAG GA  116 H28D(+16-05) CUU ACA UCU AGC ACC UCA GAG  117 H29A(+57+81) UCC GCC AUC UGU UAG GGU CUG UGC C  118 H29A(+18+42) AUU UGG GUU AUC CUC UGA AUG UCC C  119 H29D(+17-05) CAU ACC UCU UCA UGU AGU UCC C  120 H30A(+122+147) CAU UUG AGC UCG UCG CAC CUU UCC  121 H30A(+25+50) UCC UGG GCA GAC UGG AUG CUC UGU UCC  122 H30D(+19-04) UUG CCU GGG CUU CCU GAG GCA UU  123 H31D(+06-18) UUC UGA AAU AAC AUA UAC CUG UGC  124 H31D(+03-22) UAG UUU CUG AAA UAA CAU AUA CCU G  125 H31A(+05+25) GAC UUG UCA AAU CAG AUU GGA  126 H31D(+04-20) GUU UCU GAA AUA ACA UAU ACC UGU  127 H32D(+04-16) CAC CAG AAA UAC AUA CCA CA   | 104 H24A(-02+22)   |                                    |
| 106 H25A(+131+156) CUG UUG GCA CAU GUG AUC CCA CUG AG 107 H25D(+16-08) GUC UAU ACC UGU UGG CAC AUG UGA 108 H26A(+132+156) UGC UUU CUG UAA UUC AUC UGG AGU U 109 H26A(-07+19) CCU CCU UUC UGG CAU AGA CCU UCC AC 110 H26A(+68+92) UGU GUC AUC CAU UCG UGC AUC UCU G 111 H27A(+82+106) UUA AGG CCU CUU GUG CAC CAG GUG G 112 H27A(-4+19) GGG GCU CUU CUU UAG CUC UCU GA 113 H27D(+19-03) GAC UUC CAA AGU CUU GCA UUU C 114 H28A(+99+124) CAG AGA UUU CCU CAG CUC CGC CAG GA 115 H28A(+99+124) CAG AGA UUU CCU CAG CUC CGC CAG GA 116 H28D(+16-05) CUU ACA UCU AGG ACC UCA GAG 117 H29A(+57+81) UCC GCC AUC UGU UAG GGU CUG UGC C 118 H29A(+18+42) AUU UGG GUU AUC CUC UGA AUG UCC C 119 H29D(+17-05) CAU ACC UCU UCA UGU AGU UCC C 120 H30A(+122+147) CAU UUG AGC UCC UGA GAC UCC UCG UGC C 121 H30A(+25+50) UCC UGG GCA GAC UGG AUG UCC UGU UCC 122 H30D(+19-04) UUG CCU GGG CUU CCU GAG GCA UU 123 H31D(+06-18) UUC UGA AAU AAC AUA UAC CUG UGC 124 H31D(+03-22) UAG UUU CUG AAA UAA CAU AUA CCU GG 125 H31A(+05+25) GAC UUG UCA AAU CACA UAU ACC UGU 127 H32D(+04-16) CAC CAG AAA UAC AUA CCA CA  | 105 H25A(+9+36)    |                                    |
| GUC UAU ACC UGU UGG CAC AUG UGA  108 H26A(+132+156)  UGC UUU CUG UAA UUC AUC UGG AGU U  109 H26A(-07+19)  CCU CCU UUC UGG CAU AGA CCU UCC AC  110 H26A(+68+92)  UGU GUC AUC CAU UCG UGC AUC UCU GC  111 H27A(+82+106)  UUA AGG CCU CUU GUG CUA CAG GUG G  112 H27A(-4+19)  GGG GCU CUU CUU UAG CUC UCU GA  113 H27D(+19-03)  GAC UUC CAA AGU CUU GCA UUU C  114 H28A(-05+19)  GCC AAC AUG CCC AAA CUU CCU AAG  115 H28A(+99+124)  CAG AGA UUU CCU CAG CUC CGC CAG GA  116 H28D(+16-05)  CUU ACA UCU AGC ACC UCA GAG  117 H29A(+57+81)  UCC GCC AUC UGU UAG GGU CUG UGC C  118 H29A(+18+42)  AUU UGG GUU AUC CUC UGA AUG UCC C  120 H30A(+122+147)  CAU UUG AGC UCU UCA UGU AGU UCC C  121 H30A(+25+50)  UCC UGG GCA GAC UGG AUG CUC UGU UC  122 H30D(+19-04)  UUC UGA AAU AAC AUA UAC CUC UGA  124 H31D(+06-18)  UUC UGA AAU CAG AUA UAA CAU AUA CCU G  125 H31A(+05+25)  GAC UUG GAA AUA ACA UAU ACC UGU  127 H32D(+04-16)  CAC CAG AAA UAC AUA CCA CA  | 106 H25A(+131+156) |                                    |
| 108 H26A(+132+156) UGC UUU CUG UAA UUC AUC UGG AGU U 109 H26A(-07+19) CCU CCU UUC UGG CAU AGA CCU UCC AC 110 H26A(+68+92) UGU GUC AUC CAU UCG UGC AUC UCU G 111 H27A(+82+106) UUA AGG CCU CUU GUG CUA CAG GUG G 112 H27A(-4+19) GGG GCU CUU CUU UAG CUC UCU GA 113 H27D(+19-03) GAC UUC CAA AGU CUU GCA UUU C 114 H28A(-05+19) GCC AAC AUG CCC AAA CUU CCU AAG 115 H28A(+99+124) CAG AGA UUU CCU CAG CUC CGC CAG GA 116 H28D(+16-05) CUU ACA UCU AGC ACC UCA GAG 117 H29A(+57+81) UCC GCC AUC UGU UAG GGU CUG UGC C 118 H29A(+18+42) AUU UGG GUU AUC CUC UGA AUG UCC C 120 H30A(+122+147) CAU UUG AGC UCC UGA AUG UCC C 121 H30A(+25+50) UCC UGG GCA GAC UGG GCA UU 122 H30D(+19-04) UUG CCU GGG CUU CCU GAG GCA UU 123 H31D(+06-18) UUC UGA AAU AAC AUA UAC CUU GA 124 H31D(+03-22) UAG UUU CUG AAAU CAG AUU GGA 127 H32D(+04-20) GUU UCU GAA AUA ACA UAU ACC UGU 127 H32D(+04-16) CAC CAG AAA UAA CAU AUA CCU CGC 127 H32D(+04-16) CAC CAG AAA UAA CAU AUA CCU CGC 127 H32D(+04-16) CAC CAG AAA UAA CAU AUA CCU CGC 127 H32D(+04-16) CAC CAG AAA UAA CAU AUA CCU CGC 127 H32D(+04-16) CAC CAG AAA UAA CAU AUA CCU CGC 127 H32D(+04-16) CAC CAG AAA UAA CAU AUA CCU CGC 127 H32D(+04-16) CAC CAG AAA UAA CAU AUA CCA CAC  | 107 H25D(+16-08)   |                                    |
| CCU CCU UUC UGG CAU AGA CCU UCC AC  110 H26A(+68+92)  UGU GUC AUC CAU UCG UGC AUC UCU G  111 H27A(+82+106)  UUA AGG CCU CUU GUG CUA CAG GUG G  112 H27A(-4+19)  GGG GCU CUU CUU UAG CUC UCU GA  113 H27D(+19-03)  GAC UUC CAA AGU CUU GCA UUU C  114 H28A(-05+19)  GCC AAC AUG CCC AAA CUU CCU AAG  115 H28A(+99+124)  CAG AGA UUU CCU CAG CUC CGC CAG GA  116 H28D(+16-05)  CUU ACA UCU AGC ACC UCA GAG  117 H29A(+57+81)  UCC GCC AUC UGU UAG GGU CUG UGC C  118 H29A(+18+42)  AUU UGG GUU AUC CUC UGA AUG UCC C  119 H29D(+17-05)  CAU ACC UCU UCA UGU AGU UCC C  120 H30A(+122+147)  CAU UUG AGC UGC GUC CAC CUU GUC UG  121 H30A(+25+50)  UCC UGG GCA GAC UGG AUG CUC UGU UCC  122 H30D(+19-04)  UUG CCU GGG CUU CCU GAG GCA UU  123 H31D(+06-18)  UUC UGA AAU AAC AUA UAC CUU GGA  244 H31D(+03-22)  UAG UUU CUG AAA UAA CAU AUA CCU G  GAC H31D(+04-20)  GUU UCU GAA AUA ACA UAU ACC UGU  27 H32D(+04-16)  CAC CAG AAA UAC AUA CCA CA   | 108 H26A(+132+156) |                                    |
| UGU GUC AUC CAU UCG UGC AUC UCU G  111 H27A(+82+106)  UUA AGG CCU CUU GUG CUA CAG GUG G  112 H27A(-4+19)  GGG GCU CUU CUU UAG CUC UCU GA  113 H27D(+19-03)  GAC UUC CAA AGU CUU GCA UUU C  114 H28A(-05+19)  GCC AAC AUG CCC AAA CUU CCU AAG  115 H28A(+99+124)  CAG AGA UUU CCU CAG CUC CGC CAG GA  116 H28D(+16-05)  CUU ACA UCU AGC ACC UCA GAG  117 H29A(+57+81)  UCC GCC AUC UGU UAG GGU CUG UGC C  118 H29A(+18+42)  AUU UGG GUU AUC CUC UGA AUG UCC C  119 H29D(+17-05)  CAU ACC UCU UCA UGU AGU UCC C  120 H30A(+122+147)  CAU UUG AGC UGC GUC CAC CUU GUC UG  121 H30A(+25+50)  UCC UGG GCA GAC UGG AUG CUC UGU UC  122 H30D(+19-04)  UUG CCU GGG CUU CCU GAG GCA UU  123 H31D(+06-18)  UUC UGA AAU AAC AUA UAC CUC UG  25 H31A(+05+25)  GAC UUG UCA AAU CAG AUU GGA  GUU UCU GAA AUA ACA UAU ACC UGU  17 H32D(+04-20)  GUU UCU GAA AUA ACA UAU ACC UGU  17 H32D(+04-16)  CAC CAG AAA UAC AUA CCA CA  | 109 H26A(-07+19)   |                                    |
| 111 H27A(+82+106)  112 H27A(-4+19)  113 H27D(+19-03)  114 H28A(-05+19)  115 H28A(+99+124)  116 H28D(+16-05)  117 H29A(+57+81)  118 H29A(+18+42)  119 H29D(+17-05)  120 H30A(+122+147)  121 H30A(+25+50)  122 H30D(+19-04)  123 H31D(+06-18)  124 H31D(+03-22)  125 H31A(+05+25)  126 GGG GCU CUU CUU UAG CUA CAG CUC GGA  127 H32D(+04-16)  128 GGG GCU CUU CAA AGU CUU GCA UUU CCU AAG  129 GCC AAC AUG CCC AAA CUU CCU GA AGG  120 CAC UCU ACA UCU AGC ACC UCA GAG  121 H29A(+57+81)  122 GCC AUC UGU UAG GGU CUG UGC C  123 H31D(+06-18)  124 H31D(+03-22)  125 H31A(+05+25)  126 GCC AUC UCU GAA AUA CAU AUA CCU G  127 H32D(+04-16)  128 CCC CAC AUC UCU CAA AUA CCA CAC  | 110 H26A(+68+92)   |                                    |
| GAC UUC CAA AGU CUU GCA UUU C  114 H28A(-05+19) GCC AAC AUG CCC AAA CUU CCU AAG  115 H28A(+99+124) CAG AGA UUU CCU CAG CUC CGC CAG GA  116 H28D(+16-05) CUU ACA UCU AGC ACC UCA GAG  117 H29A(+57+81) DCC GCC AUC UGU UAG GGU CUG UGC C  118 H29A(+18+42) AUU UGG GUU AUC CUC UGA AUG UCG C  119 H29D(+17-05) CAU ACC UCU UCA UGU AGU UCC C  120 H30A(+122+147) CAU UUG AGC UGC GUC CAC CUU GUC UG  121 H30A(+25+50) UCC UGG GCA GAC UGG AUG CUC UGU UC  122 H30D(+19-04) UUG UGA AAU AAC AUA UAC CUU GC  134 H31D(+06-18) UAG UUU CUG AAA UAA CAU AUA CCU G  135 H31A(+05+25) GAC UUG UCA AAU CAG AUU GGA  146 H31D(+04-20) CAC CAG AAA UAC AUA CCA CA  | 111 H27A(+82+106)  |                                    |
| GCC AAC AUG CCC AAA CUU CCU AAG  115 H28A(+99+124)  CAG AGA UUU CCU CAG CUC CGC CAG GA  116 H28D(+16-05)  CUU ACA UCU AGC ACC UCA GAG  117 H29A(+57+81)  UCC GCC AUC UGU UAG GGU CUG UGC C  118 H29A(+18+42)  AUU UGG GUU AUC CUC UGA AUG UCG C  119 H29D(+17-05)  CAU ACC UCU UCA UGU AGU UCC C  120 H30A(+122+147)  CAU UUG AGC UGC GUC CAC CUU GUC UG  121 H30A(+25+50)  UCC UGG GCA GAC UGG AUG CUC UGU UC  122 H30D(+19-04)  UUC UGA AAU AAC AUA UAC CUG UGC  123 H31D(+06-18)  UUC UGA AAU AAC AUA UAC CUU GGA  125 H31A(+05+25)  GAC UUG UCA AAU CAG AUU GGA  127 H32D(+04-16)  CAC CAG AAA UAC AUA CCA CA  | 112 H27A(-4+19)    | GGG GCU CUU CUU UAG CUC UCU GA     |
| CAG AGA UUU CCU CAG CUC CGC CAG GA  116 H28D(+16-05)  CUU ACA UCU AGC ACC UCA GAG  117 H29A(+57+81)  DCC GCC AUC UGU UAG GGU CUG UGC C  118 H29A(+18+42)  AUU UGG GUU AUC CUC UGA AUG UCG C  119 H29D(+17-05)  CAU ACC UCU UCA UGU AGU UCC C  120 H30A(+122+147)  CAU UUG AGC UGC GUC CAC CUU GUC UG  121 H30A(+25+50)  UCC UGG GCA GAC UGG AUG CUC UGU UC  122 H30D(+19-04)  UUG UGA AAU AAC AUA UAC CUG UGC  124 H31D(+06-18)  UAG UUU CUG AAA UAA CAU AUA CCU G  125 H31A(+05+25)  GAC UUG UCA AAU CAG AUU GGA  126 H31D(+04-20)  GUU UCU GAA AUA ACA UAU ACC UGU  127 H32D(+04-16)  CAC CAG AAA UAC AUA CCA CA   | 113 H27D(+19-03)   | GAC UUC CAA AGU CUU GCA UUU C      |
| CUU ACA UCU AGC ACC UCA GAG  117 H29A(+57+81)  UCC GCC AUC UGU UAG GGU CUG UGC C  118 H29A(+18+42)  AUU UGG GUU AUC CUC UGA AUG UCG C  119 H29D(+17-05)  CAU ACC UCU UCA UGU AGU UCC C  120 H30A(+122+147)  CAU UUG AGC UGC GUC CAC CUU GUC UG  121 H30A(+25+50)  UCC UGG GCA GAC UGG AUG CUC UGU UC  122 H30D(+19-04)  UUC UGA AAU AAC AUA UAC CUG UGC  123 H31D(+06-18)  UUC UGA AAU AAC AUA UAC CUG UGC  125 H31A(+05+25)  GAC UUG UCA AAU CAG AUU GGA  126 H31D(+04-20)  GUU UCU GAA AUA ACA UAU ACC UGU  CAC CAG AAA UAC AUA CCA CA   | 114 H28A(-05+19)   | GCC AAC AUG CCC AAA CUU CCU AAG    |
| 117 H29A(+57+81) DCC GCC AUC UGU UAG GGU CUG UGC C 118 H29A(+18+42) AUU UGG GUU AUC CUC UGA AUG UCG C 119 H29D(+17-05) CAU ACC UCU UCA UGU AGU UCC C 120 H30A(+122+147) CAU UUG AGC UGC GUC CAC CUU GUC UG 121 H30A(+25+50) UCC UGG GCA GAC UGG AUG CUC UGU UC 122 H30D(+19-04) UUG CCU GGG CUU CCU GAG GCA UU 123 H31D(+06-18) UUC UGA AAU AAC AUA UAC CUG UGC 124 H31D(+03-22) UAG UUU CUG AAA UAA CAU AUA CCU G 125 H31A(+05+25) GAC UUG UCA AAU CAG AUU GGA 126 H31D(+04-20) GUU UCU GAA AUA ACA UAU ACC UGU 127 H32D(+04-16) CAC CAG AAA UAC AUA CCA CA   | 115 H28A(+99+124)  | CAG AGA UUU CCU CAG CUC CGC CAG GA |
| AUU UGG GUU AUC CUC UGA AUG UCG C L19 H29D(+17-05) CAU ACC UCU UCA UGU AGU UCC C L20 H30A(+122+147) CAU UUG AGC UGC GUC CAC CUU GUC UG L21 H30A(+25+50) UCC UGG GCA GAC UGG AUG CUC UGU UC L22 H30D(+19-04) UUG CCU GGG CUU CCU GAG GCA UU L23 H31D(+06-18) UUC UGA AAU AAC AUA UAC CUG UGC L24 H31D(+03-22) UAG UUU CUG AAA UAA CAU AUA CCU G L25 H31A(+05+25) GAC UUG UCA AAU CAG AUU GGA L27 H32D(+04-16) CAC CAG AAA UAC AUA CCA CA  | 116 H28D(+16-05)   | CUU ACA UCU AGC ACC UCA GAG        |
| CAU ACC UCU UCA UGU AGU UCC C  L20 H30A(+122+147)  CAU UUG AGC UGC GUC CAC CUU GUC UG  L21 H30A(+25+50)  UCC UGG GCA GAC UGG AUG CUC UGU UC  L22 H30D(+19-04)  UUG CCU GGG CUU CCU GAG GCA UU  UUC UGA AAU AAC AUA UAC CUG UGC  L24 H31D(+06-18)  UAG UUU CUG AAA UAA CAU AUA CCU G  L25 H31A(+05+25)  GAC UUG UCA AAU CAG AUU GGA  L26 H31D(+04-20)  GUU UCU GAA AUA ACA UAU ACC UGU  CAC CAG AAA UAC AUA CCA CA  | 117 H29A(+57+81)   | UCC GCC AUC UGU UAG GGU CUG UGC C  |
| CAU UUG AGC UGC GUC CAC CUU GUC UG  C21 H30A(+25+50)  UCC UGG GCA GAC UGG AUG CUC UGU UC  C22 H30D(+19-04)  UUG CCU GGG CUU CCU GAG GCA UU  C33 H31D(+06-18)  UUC UGA AAU AAC AUA UAC CUG UGC  UAG UUU CUG AAA UAA CAU AUA CCU G  C55 H31A(+05+25)  C60 H31D(+04-20)  C7 H32D(+04-16)  CAC CAG AAA UAC AUA CCA CA  | 118 H29A(+18+42)   | AUU DGG GUU AUC CUC UGA AUG UCG C  |
| 22 H30A(+122+147) CAU UUG AGC UGC GUC CAC CUU GUC UG 21 H30A(+25+50) UCC UGG GCA GAC UGG AUG CUC UGU UC 22 H30D(+19-04) UUG CCU GGG CUU CCU GAG GCA UU 23 H31D(+06-18) UUC UGA AAU AAC AUA UAC CUG UGC 24 H31D(+03-22) UAG UUU CUG AAA UAA CAU AUA CCU G 25 H31A(+05+25) GAC UUG UCA AAU CAG AUU GGA 26 H31D(+04-20) GUU UCU GAA AUA ACA UAU ACC UGU 27 H32D(+04-16) CAC CAG AAA UAC AUA CCA CA  | (19 H29D(+17-05)   | CAU ACC UCU UCA UGU AGU UCC C      |
| 22 H30D(+19-04)  DUG CCU GGG CUU CCU GAG GCA UU  23 H31D(+06-18)  UUC UGA AAU AAC AUA UAC CUG UGC  24 H31D(+03-22)  UAG UUU CUG AAA UAA CAU AUA CCU G  25 H31A(+05+25)  GAC UUG UCA AAU CAG AUU GGA  26 H31D(+04-20)  GUU UCU GAA AUA ACA UAU ACC UGU  27 H32D(+04-16)  CAC CAG AAA UAC AUA CCA CA   | L20 H30A(+122+147) | CAU UUG AGC UGC GUC CAC CUU GUC UG |
| 122 H30D(+19-04)  123 H31D(+06-18)  124 H31D(+03-22)  125 H31A(+05+25)  126 H31D(+04-20)  127 H32D(+04-16)  128 CCU GGG CUU CCU GAG GCA UU  129 UCU GAA AUA CAU AUA CCU G  120 UCU GAA AUA CAG AUU GGA  120 UCU GAA AUA ACA UAU ACC UGU  127 H32D(+04-16)  128 CAG AAA UAC AUA CCA CA  | 21 H30A(+25+50)    | UCC UGG GCA GAC UGG AUG CUC UGU UC |
| 23 H31D(+06-18) UUC UGA AAU AAC AUA UAC CUG UGC 24 H31D(+03-22) UAG UUU CUG AAA UAA CAU AUA CCU G 25 H31A(+05+25) GAC UUG UCA AAU CAG AUU GGA 26 H31D(+04-20) GUU UCU GAA AUA ACA UAU ACC UGU 27 H32D(+04-16) CAC CAG AAA UAC AUA CCA CA   |                    | DUG CCU GGG CUU CCU GAG GCA UU     |
| 24 H31D(+03-22) UAG UUU CUG AAA UAA CAU AUA CCU G 25 H31A(+05+25) GAC UUG UCA AAU CAG AUU GGA 26 H31D(+04-20) GUU UCU GAA AUA ACA UAU ACC UGU 27 H32D(+04-16) CAC CAG AAA UAC AUA CCA CA   |                    |                                    |
| 25 H31A(+05+25) GAC UUG UCA AAU CAG AUU GGA<br>26 H31D(+04-20) GUU UCU GAA AUA ACA UAU ACC UGU<br>27 H32D(+04-16) CAC CAG AAA UAC AUA CCA CA   |                    |                                    |
| 26 H31D(+04-20) GUU UCU GAA AUA ACA UAU ACC UGU<br>27 H32D(+04-16) CAC CAG AAA UAC AUA CCA CA  |                    |                                    |
| 27 H32D(+04-16) CAC CAG AAA UAC AUA CCA CA   |                    |                                    |
|  |                    |                                    |
| 28 H32A(+151+170) CAA UGA UUU AGC UGU GAC UG   |                    |                                    |
| 29 H32A(+10+32) CGA AAC UUC AUG GAG ACA UCU UG   |                    |                                    |

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# TABLE 1A-continued

Description of 2'-O-methyl phosphorothicate antisense oligonuclectides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonuclectides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| ID SEQUENCE  | NUCLEOTIDE SEQUENCE (5'-3')                |
|--|--|
| 130 H32A(+49+73)   | CUU GUA GAC GCU GCU CAA AAU UGG C          |
| 131 H33D(+09-11)   | CAU GCA CAC ACC UUU GCU CC                 |
| 132 H33A(+53+76)   | UCU GUA CAA UCU GAC GUC CAG UCU            |
| 133 H33A(+30+56)   | GUC UUU AUC ACC AUU UCC ACU UCA GAC        |
| 134 H33A(+64+88)   | CCG UCU GCD UUU UCU GUA CAA UCU G          |
| 135 H34A(+83+104)  |  |
| 136 H34A(+143+165)   |  |
| 137 H34A(-20+10)   | UUU CUG UUA CCU GAA AAG AAU UAU AAU<br>GAA |
| 138 H34A(+46+70)   | CAU UCA UUU CCU UUC GCA UCU UAC G          |
| 139 H34A(+95+120)  |  |
| 140 H34D(+10-20)   | UUC AGU GAU AUA GGU UUU ACC UUU CCC<br>CAG |
| 141 H34A(+72+96)   | CUG UAG CUG CCA GCC AUU CUG UCA AG         |
| 142 H35A(+141+161)   | UCU UCU GCU CGG GAG GUG ACA                |
| 143 H35A(+116+135)   | CCA GUU ACU AUU CAG AAG AC                 |
| 144 H35A(+24+43)   | UCU UCA GGU GCA CCU UCU GU                 |
| 145 H36A(+26+50)   | UGU GAU GUG GUC CAC AUU CUG GUC A          |
| 146 H36A(-02+18)   | CCA UGU GUU UCU GGU AUU CC                 |
| 147 H37A(+26+50)   | CGU GUA GAG UCC ACC UUU GGG CGU A          |
| 148 H37A(+82+105)  | UAC UAA UUU CCU GCA GUG GUC ACC            |
| 149 H37A(+134+157)   | UUC UGU GUG AAA UGG CUG CAA AUC            |
| 150 H38A(-01+19)   | CCU UCA AAG GAA UGG AGG CC                 |
| 151 H38A(+59+83)   | UGC UGA AUU UCA GCC UCC AGU GGU U          |
| .52 H38A(+88+112)  | UGA AGU CUU CCU CUU UCA GAU UCA C          |
| .53 H39A(+62+85)   | CUG GCU UUC UCU CAU CUG UGA UUC            |
| 54 H39A(+39+58)  | GUU GUA AGU UGU CUC CUC UU                 |
| 55 H39A(+102+121)  | UUG UCU GUA ACA GCU GCU GU                 |
| The state of the s | GCU CUA AUA CCU UGA GAG CA                 |
|  | CUU UGA GAC CUC AAA UCC UGU U              |
|  | CUU UAU UUU CCU UUC AUC UCU GGG C          |
|  | AUC GUU UCU UCA CGG ACA GUG UGC UGG        |
|  | GGG CUU GUG AGA CAU GAG UGA UUU            |
|  | A CCU UCA GAG GAC UCC UCU UGC              |
|  | UAU GUG UUA CCU ACC CUU GUC GGU C          |
|  |  |
| 53 H43A(+101+120)  | GGA GAG AGC UUC CUG UAG CU                 |

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# TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ    | SEQUENCE                | NUCLEOTIDE SEQUENCE (5'-3')                        |
|--------|-------------------------|--|
| 164    | H43A(+78+100)           | UCA CCC UUU CCA CAG GCG UUG CA                     |
| 165    | H44A(+85+104)           | UUU GUG UCU UUC UGA GAA AC                         |
| 166    | H44D(+10-10)            | AAA GAC UUA CCU UAA GAU AC                         |
| 167    | H44A(-06+14)            | AUC UGU CAA AUC GCC UGC AG                         |
| 168    | H46D(+16-04)            | UUA CCU UGA CUU GCU CAA GC                         |
| 169    | H46A(+90+109)           | UCC AGG UUC AAG UGG GAU AC                         |
| 170    | H47A(+76+100)           | GCU CUU CUG GGC UUA UGG GAG CAC U                  |
| 171    | H47D(+25-02)            | ACC UUU AUC CAC UGG AGA UUU GUC UGC                |
| 172    | H47A(-9+12)             | UUC CAC CAG UAA CUG AAA CAG                        |
| 173    | H50A(+02+30)            | CCA CUC AGA GCU CAG AUC UUC UAA CUU CC             |
| 174 1  | 350A(+07+33)            | CUU CCA CUC AGA GCU CAG AUC UUC UAA                |
| 175 F  | H50D(+07-18)            | GGG AUC CAG UAU ACU UAC AGG CUC C                  |
| 176 F  | IS1A (-01+25)           | ACC AGA GUA ACA GUC UGA GUA GGA GC                 |
| 177 H  | (51D(+16-07)            | CUC AUA CCU UCU GCU UGA UGA UC                     |
| 178 H  | 51A(+111 +134)          | UUC UGU CCA AGC CCG GUU GAA AUC                    |
| 179 H  | 51A(+61+90)             | ACA UCA AGG AAG AUG GCA UUU CUA GUU<br>UGG         |
| 180 H  | 51A(+66+90)             | ACA UCA AGG AAG AUG GCA UUU CUA G                  |
| 181 H  | 51A(+66+95)             | CUC CAA CAU CAA GGA AGA UGG CAU UUC<br>UAG         |
| 182 H  | 51D(+08-17)             | AUC AUU UUU UCU CAU ACC UUC UGC U                  |
|        | 51A/D(+08-17)<br>(-15+) | AUC AUU UUU UCU CAU ACC UUC UGC UAG<br>GAG CUA AAA |
| 184 HS | 51A(+175+195)           | CAC CCA CCA UCA CCC UCU GUG                        |
| 185 HS | 51A(+199+220)           | AUC AUC UCG UUG AUA UCC UCA A                      |
| 186 HS | 52A(-07+14)             | UCC UGC AUU GUU GCC UGU AAG                        |
| 187 HS |                         | UCC AAC UGG GGA CGC CUC UGU UCC AAA                |
| 188 H5 | 2A(+17+37)              | ACU GGG GAC GCC UCU GUU CCA                        |
|        |                         | CCG UAA UGA UUG UUC UAG CC                         |
|        |                         | UGU WAA AAA ACU WAC UUC GA                         |
|        |                         | CAU UCA ACU GUU GCC UCC GGU UCU G                  |

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# TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

|     | Q<br>D | SEQUENCE       | NU  | CLEO | TIDE  | SEQ   |     |       |     |     | as "T". |
|-----|--------|----------------|-----|------|-------|-------|-----|-------|-----|-----|---------|
| 19  | 2      | H53A(+39+62)   |     |      |       | u ccc |     |       |     |     |         |
| 19  | 3      | H53A(+39+69)   | CA  |      |       |       |     |       |     |     | GAA     |
| 19  | 4      | H53D(+14-07)   | UA  | UAJ  | A CCI | J UGO | טטנ | CUG   | UGA |     |         |
| 19  | 5      | H53A(+23+47)   |     |      |       | טטט   |     |       |     |     | C       |
| 19  | 6      | H53A(+150+176) |     |      |       |       |     |       |     |     | cuc     |
| 19  | 7      | H53D(+20-05)   |     |      |       | GUU   |     |       |     |     |         |
| 198 | 8      | H53D(+09-18)   |     |      |       |       |     |       |     |     | unc     |
| 199 | 9 1    | H53A(-12+10)   |     |      |       | ACU   |     |       |     |     |         |
| 200 | ) 1    | H53A(-07+18)   | GAU | UCU  | GAA   | מטכ   | טטט | CAA   | CUA | GAA | U       |
| 201 | 1      | H53A(+07+26)   | AUC | CCA  | CUG   | AUU   | CUG | AAU   | UC  |     |         |
| 202 | I      | H53A(+124+145) | UUG | GCU  | CUG   | GCC   | UGU | ccu   | AAG | A   |         |
| 203 | ŀ      | H46A(+86+115)  | CUC | טטט  | UCC   | AGG   | DUC | AAG   | UGG | GAU | ACU     |
| 204 | Н      | H46A(+107+137) | CAA |      | טטט   | cuu   | UUA | GUU   | GCU | GCU | cuu     |
| 205 | Н      | 446A(-10+20)   | UAU | ucu  | טטט   | GUU   | cuu | CUA   | GCC | UGG | AGA     |
| 206 | Н      | 46A(+50+77)    | CUG | CUU  | CCU   | CCA   | ACC | AUA   | AAA | CAA | AUU C   |
| 207 | Н      | 45A(-06+20)    | CCA | AUG  | CCA   | UCC   | UGG | AGU   | ucc | UGU | AA      |
| 208 | Н      | 45A(+91 +110)  | ucc | UGU  | AGA   | AUA   | CUG | GCA   | UC  |     |         |
| 209 | H      | 45A(+125+151)  | UGC | AGA  | CCU   | ccu   | GCC | ACC   | GCA | GAU | UCA     |
| 210 | Н      | 45D(+16 -04)   | CUA | CCU  | cuu   | טטט   | ucu | GUC   | UG  |     |         |
| 211 | Н      | 45A(+71+90)    | UGU | טטט  | UGA   | GGA   | UUG | cug : | AA  |     |         |

#### TABLE 1B

Description of a cocktail of 2'-0-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

| SEQ<br>ID SEQUENCE                 | NUC | LEOT     | IDE | SEQU | ENCE | (5) | -3') |     |  |
|------------------------------------|-----|----------|-----|------|------|-----|------|-----|--|
| 81 H20A(+44+71)                    | CUG | GCA      | GAA | uuc  | GAU  | CCA | CCG  | gcu |  |
| 82 H20A(+147+168)                  | GUU | CAG      | UAG | UUG  | UCA  | ncn | GCU  | c   |  |
| 80 H19A(+35+65)<br>81 H20A(+44+71) | GCC | UGA      | GCU | GAU  | CUG  | CUG | GCA  | UCU |  |
| 82 H20A(+147+168)                  |     | U<br>GCA | GAA | UUC  | GAU  | CCA | CCG  | GCU |  |
|                                    | GUU | C<br>CAG | UAG | nnd  | UCA  | UCU | GCU  | C   |  |

#### TABLE 1B-continued

Description of a cocktail of 2'-0-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

|    | SEQ<br>ID SEQUENCE | NUC | LEOT | IDE : | SEQU | ENCE | (51 | -3') |     |
|----|--------------------|-----|------|-------|------|------|-----|------|-----|
| 60 | 194H53D(+14-07)    | UAC | UAA  | CCU   | UGG  | טטט  | CUG | UGA  |     |
|    | 195H53A(+23+47)    | CUG | AAG  | GUG   | UUC  | UUG  | UAC | UUC  | AUC |
| 5  | 196H53A(+150+175)  | UGU | AUA  | GGG   | ACC  | CUC  | CUU | CCA  | UGA |

TABLE 1C

Description of a "weasel" of 2'-0-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mnna

| SE  | Q<br>SEQUENCE           | NUCLEOTIDE SEQUENCE (5'-3')                |
|-----|-------------------------|--|
|     | 1 H2OA(+44+71) -        | CUG GCA GAR MUG GRU TO                     |
| 8   | 2 H20A(+147+168)        | CAG CAG UAG UUG UCA UCU GCU C              |
|     | H19A(+35+65)-           | GCC UGA GCU GAU CUG CUG GCA UCU UGC        |
| 8,8 | H20A(+44+63) -          | -AUU CGA UCC ACC GGC UGU UC-               |
| 75  | H20A(+149+168)          | CUG CUG GCA UCU UGC AGU U                  |
|     | H19A(+35+65)-           | GCC UGA GCU GAU CUG CUG GCA UCU UGC        |
| 88  | H20A(+44+63)            | -AUU CGA UCC ACC GGC UGU UC-               |
| 80  | H19A(+35+65) -          | GCC UGA GCU GAU CUG CUG GCA UCU UGC        |
| 79  | H20A(+149+168)          | -CUG CUG GCA DCU UGC AGU U                 |
| 138 | H34A(+46+70) -          | CAU UCA UUU CCU UUC GCA UCU UAC G-         |
| 139 | H34A(+94+120)           | UGA UCU CUU UGU CAA UUC CAU AUC UG         |
|     | H31D(+03-22) -<br>UU-   | UAG UUU CUG AAA UAA CAU AUA CCU G-         |
| 44  | H35A(+24+43)            | UCU UCA GGU GCA CCU UCU GU                 |
| 95  | H53A(+23+47) -<br>AA-   | CUG AAG GUG UUC UUG UAC UUC AUC C-         |
| 96  | H53A(+150+175) -<br>AA- | UGU AUA GGG ACC CUC CUU CCA UGA CUC-       |
| 94  | H53D(+14-07)            | UAC UAA CCU UGG UUU CUG UGA                |
| -   | Aimed at exons          | CAG CAG UAG UUG UCA UCU GCU CAA CUG        |
| 12  | 19/20/20                | GCA GAA UUC GAU CCA CCG GCU GUU CAA        |
| -   |                         | GCC UGA GCU GAU CUG CUC GCA UCU<br>UGC AGU |

# DETAILED DESCRIPTION OF THE INVENTION

General

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variation and 45 modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally equivalent products, compositions and methods are clearly within the scope of the invention as described herein.

Sequence identity numbers (SEQ ID NO:) containing nucleotide and amino acid sequence information included in this specification are collected at the end of the description and have been prepared using the programme Patentin Version 3.0. Each nucleotide or amino acid sequence is identified in the sequence listing by the numeric indicator <210> followed by the sequence identifier (e.g. <210>1, <210>2, etc.). The length, type of sequence and source organism for each nucleotide or amino acid sequence are indicated by information provided in the numeric indicator 65 fields <211>, <212> and <213>, respectively. Nucleotide and amino acid sequences referred to in the specification are

defined by the information provided in numeric indicator field <400> followed by the sequence identifier (e.g. 400>1, <400>2, etc.).

An antisense molecules nomenclature system was proposed and published to distinguish between the different antisense molecules (see Mann et al., (2002) *J Gen Med* 4, 644-654). This nomenclature became especially relevant when testing several slightly different antisense molecules, all directed at the same target region, as shown below:

H#A/D(x:v).

The first letter designates the species (e.g. H: human, M: 50 rnurine, C: canine) "#" designates target dystrophin exon number.

"A/D" indicates acceptor or donor splice site at the beginning and end of the exon, respectively.

(x y) represents the annealing coordinates where "-" or "+" indicate intronic or exonic sequences respectively. As an example, A(-6+18) would indicate the last 6 bases of the intron preceding the target exon and the first 18 bases of the target exon. The closest splice site would be the acceptor so these coordinates would be preceded with an "A". Describing annealing coordinates at the donor splice site could be D(+2-18) where the last 2 exonic bases and the first 18 intronic bases correspond to the annealing site of the antisense molecule. Entirely exonic annealing coordinates that would be represented by A(+65+85), that is the site between the 65th and 85th nucleotide from the start of that exon.

The entire disclosures of all publications (including patents, patent applications, journal articles, laboratory manu-

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als, books, or other documents) cited herein are hereby incorporated by reference. No admission is made that any of the references constitute prior art or are part of the common general knowledge of those working in the field to which this invention relates.

As used necessarily herein the term "derived" and "derived from" shall be taken to indicate that a specific integer may be obtained from a particular source albeit not directly from that source.

Throughout this specification, unless the context requires to otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Other definitions for selected terms used herein may be 15 found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

### Description of the Preferred Embodiment

When antisense molecule(s) are targeted to nucleotide sequences involved in splicing in exons within pre-mRNA 25 sequences, normal splicing of the exon may be inhibited causing the splicing machinery to by-pass the entire mutated exon from the mature mRNA. The concept of antisense oligonucleotide induced exon skipping is shown in FIG. 2. In many genes, deletion of an entire exon would lead to the 30 production of a non-functional protein through the loss of important functional domains or the disruption of the reading frame. In some proteins, however, it is possible to shorten the protein by deleting one or more exons, without disrupting the reading frame, from within the protein with- 35 out seriously altering the biological activity of the protein. Typically, such proteins have a structural role and or possess functional domains at their ends. The present invention describes antisense molecules capable of binding to specified dystrophin pre-mRNA targets and re-directing process- 40 ing of that gene.

Antisense Molecules

According to a first aspect of the invention, there is provided antisense molecules capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules are preferably selected from the group of compounds shown in Table 1A. There is also provided a combination or "cocktail" of two or more antisense oligonucleotides capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules in a "cocktail" are preferably selected from the group of compounds shown in Table 1B. Alternatively, exon skipping may be induced by antisense oligonucleotides joined together "weasels" preferably selected from the group of compounds shown in Table 1C.

Designing antisense molecules to completely mask consensus splice sites may not necessarily generate any skipping of the targeted exon. Furthermore, the inventors have discovered that size or length of the antisense oligonucleotide itself is not always a primary factor when designing antisense molecules. With some targets such as exon 19, antisense oligonucleotides as short as 12 bases were able to induce exon skipping, albeit not as efficiently as longer 65 (20-31 bases) oligonucleotides. In some other targets, such as murine dystrophin exon 23, antisense oligonucleotides

only 17 residues long were able to induce more efficient skipping than another overlapping compound of 25 nucleotides.

The inventors have also discovered that there does not appear to be any standard motif that can be blocked or masked by antisense molecules to redirect splicing. In some exons, such as mouse dystrophin exon 23, the donor splice site was the most amenable to target to re-direct skipping of that exon. It should be noted that designing and testing a series of exon 23 specific antisense molecules to anneal to overlapping regions of the donor splice site showed considerable variation in the efficacy of induced exon skipping. As reported in Mann et al., (2002) there was a significant variation in the efficiency of bypassing the nonsense mutation depending upon antisense oligonucleotide annealing ("Improved antisense oligonucleotide induced exon skipping in the mdx mouse model of muscular dystrophy". J Gen Med 4: 644-654). Targeting the acceptor site of exon 23 or several internal domains was not found to induce any 20 consistent exon 23 skipping.

In other exons targeted for removal, masking the donor splice site did not induce any exon skipping. However, by directing antisense molecules to the acceptor splice site (human exon 8 as discussed below), strong and sustained exon skipping was induced. It should be noted that removal of human exon 8 was tightly linked with the co-removal of exon 9. There is no strong sequence homology between the exon 8 antisense oligonucleotides and corresponding regions of exon 9 so it does not appear to be a matter of cross reaction. Rather the splicing of these two exons is inextricably linked. This is not an isolated instance as the same effect is observed in canine cells where targeting exon 8 for removal also resulted in the skipping of exon 9. Targeting exon 23 for removal in the mouse dystrophin pre-mRNA also results in the frequent removal of exon 22 as well. This effect occurs in a dose dependent manner and also indicates close coordinated processing of 2 adjacent exons.

In other targeted exons, antisense molecules directed at the donor or acceptor splice sites did not induce exon skipping while annealing antisense molecules to intra-exonic regions (i.e. exon splicing enhancers within human dystrophin exon 6) was most efficient at inducing exon skipping. Some exons, both mouse and human exon 19 for example, are readily skipped by targeting antisense molecules to a variety of motifs. That is, targeted exon skipping is induced after using antisense oligonucleotides to mask donor and acceptor splice sites or exon splicing enhancers.

To identify and select antisense oligonucleotides suitable for use in the modulation of exon skipping, a nucleic acid sequence whose function is to be modulated must first be identified. This may be, for example, a gene (or mRNA transcribed form the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (i.e. splice donor sites, splice acceptor sites, or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

Preferably, the present invention aims to provide antisense molecules capable of binding to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping. Duchenne muscular dystrophy arises from mutations that preclude the synthesis of a functional dystrophin gene product. These Duchenne muscular dystrophy gene defects are typically nonsense mutations or genomic

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rearrangements such as deletions, duplications or microdeletions or insertions that disrupt the reading frame. As the human dystrophin gene is a large and complex gene with the 79 exons being spliced together to generate a mature mRNA with an open reading frame of approximately 11,000 bases, 5 there are many positions where these mutations can occur. Consequently, a comprehensive antisense oligonucleotide based therapy to address many of the different diseasecausing mutations in the dystrophin gene will require that many exons can be targeted for removal during the splicing 10 process.

Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (i.e. splice donor sites, splice acceptor sites or exonic splicing enhancer elements). Splicing branch points and exon recognition 15 sequences or splice enhancers are also potential target sites

for modulation of mRNA splicing.

The oligonucleotide and the DNA or RNA are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleo- 20 tides which can hydrogen bond with each other. Thus, "specifically hybridisable" and "complementary" are terms which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or 25 RNA target. It is understood in the art that the sequence of an antisense molecule need not be 100% complementary to that of its target sequence to be specifically hybridisable, An antisense molecule is specifically hybridisable when binding of the compound to the target DNA or RNA molecule 30 interferes with the normal function of the target DNA or RNA to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target sequences under conditions in which specific binding is desired, i.e., under physi- 35 ological conditions in the case of in vivo assays or therapeutic treatment, and in the case of in vitro assays, under conditions in which the assays are performed.

While the above method may be used to select antisense molecules capable of deleting any exon from within a 40 protein that is capable of being shortened without affecting its biological function, the exon deletion should not lead to a reading frame shift in the shortened transcribed mRNA. Thus, if in a linear sequence of three exons the end of the first exon encodes two of three nucleotides in a codon and 45 the next exon is deleted then the third exon in the linear sequence must start with a single nucleotide that is capable of completing the nucleotide triplet for a codon. If the third exon does not commence with a single nucleotide there will be a reading frame shift that would lead to the generation of 50 truncated or a non-functional protein.

It wilt be appreciated that the codon arrangements at the end of exons in structural proteins may not always break at the end of a codon, consequently there may be a need to delete more than one exon from the pre-mRNA to ensure in-frame reading of the mRNA. In such circumstances, a plurality of antisense oligonucleotides may need to be selected by the method of the invention wherein each is directed to a different region responsible for inducing splic-

ing in the exons that are to be deleted.

The length of an antisense molecule may vary so long as it is capable of binding selectively to the intended location within the pre-mRNA molecule. The length of such sequences can be determined in accordance with selection procedures described herein. Generally, the antisense molecule will be from about 10 nucleotides in length up to about 50 nucleotides in length. It will be appreciated however that

any length of nucleotides within this range may be used in the method. Preferably, the length of the antisense molecule is between 17 to 30 nucleotides in length.

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In order to determine which exons can be connected in a dystrophin gene, reference should be made to an exon boundary map. Connection of one exon with another is based on the exons possessing the same number at the 3' border as is present at the 5' border of the exon to which it is being connected. Therefore, if exon 7 were deleted, exon 6 must connect to either exons 12 or 18 to maintain the reading frame. Thus, antisense oligonucleotides would need to be selected which redirected splicing for exons 7 to 11 in the first instance or exons 7 to 17 in the second instance. Another and somewhat simpler approach to restore the reading frame around an exon 7 deletion would be to remove the two flanking exons. Induction of exons 6 and 8 skipping should result in an in-frame transcript with the splicing of exons 5 to 9. In practise however, targeting exon 8 for removal from the pre-mRNA results in the co-removal of exon 9 so the resultant transcript would have exon 5 joined to exon 10. The inclusion or exclusion of exon 9 does not alter the reading frame. Once the antisense molecules to be tested have been identified, they are prepared according to standard techniques known in the art. The most common method for producing antisense molecules is the methylation of the 2' hydroxyribose position and the incorporation of a phosphorothioate backbone produces molecules that superficially resemble RNA but that are much more resistant to nuclease degradation.

To avoid degradation of pre-mRNA during duplex formation with the antisense molecules, the antisense molecules used in the method may be adapted to minimise or prevent cleavage by endogenous RNase H. This property is highly preferred as the treatment of the RNA with the unmethylated oligonucleotides either intracellularly or in crude extracts that contain RNase H leads to degradation of the pre-mRNA: antisense oligonucleotide duplexes. Any form of modified antisense molecules that is capable of bypassing or not inducing such degradation may be used in the present method. An example of antisense molecules which when duplexed with RNA are not cleaved by cellular RNase H is 2'-O-methyl derivatives. 2'-O-methyl-oligoribo-nucleotides are very stable in a cellular environment and in animal tissues, and their duplexes with RNA have higher Tm

values than their ribo- or deoxyribo-counterparts. Antisense molecules that do not activate RNase H can be made in accordance with known techniques (see, e.g., U.S. Pat. No. 5,149,797). Such antisense molecules, which may be deoxyribonucleotide or ribonucleotide sequences, simply contain any structural modification which sterically hinders or prevents binding of RNase H to a duplex molecule containing the oligonucleotide as one member thereof, which structural modification does not substantially hinder or disrupt duplex formation. Because the portions of the oligonucleotide involved in duplex formation are substantially different from those portions involved in RNase H binding thereto, numerous antisense molecules that do not activate RNase H are available. For example, such antisense molecules may be oligonucleotides wherein at least one, or 60 all, of the inter-nucleotide bridging phosphate residues are modified phosphates, such as methyl phosphonates, methyl phosphorothioates, phosphoromorpholidates, phosphoropiperazidates and phosphoramidates. For example, every other one of the internucleotide bridging phosphate residues may be modified as described. In another non-limiting example, such antisense molecules are molecules wherein at least one, or all, of the nucleotides contain a 2' lower alkyl

moiety (e.g.,  $C_1$ - $C_4$ , linear or branched, saturated or unsaturated alkyl, such as methyl, ethyl, ethenyl, propyl, 1-propenyl, 2-propenyl, and isopropyl). For example, every other one of the nucleotides may be modified as described.

While antisense oligonucleotides are a preferred form of 5 the antisense molecules, the present invention comprehends other oligomeric antisense molecules, including but not limited to oligonucleotide mimetics such as are described below.

Specific examples of preferred antisense compounds useful in this invention include oligonucleotides containing modified backbones or non-natural inter-nucleoside linkages. As defined in this specification, oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their inter-nucleoside backbone can also be considered to be oligonucleosides.

In other preferred oligonucleotide mimetics, both the sugar and the inter-nucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugarbackbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine 30 backbone. The nucleo-bases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone.

Modified oligonucleotides may also contain one or more substituted sugar moieties. Oligonucleotides may also 35 include nucleobase (often referred to in the art simply as "base") modifications or substitutions. Certain nucleo-bases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2° C. and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety, cholic acid, a thioether, e.g., hexyl-S-tritylthiol, a thiocholesterol, an aliphatic chain, e.g., dodecandiol or undecyl residues, a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety.

It is not necessary far all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes antisense compounds that are chimeric compounds. "Chimeric" 65 antisense compounds or "chimeras," in the context of this invention, are antisense molecules, particularly oligonucle-

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otides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the increased resistance to nuclease degradation, increased cellular uptake, and an additional region for increased binding affinity for the target nucleic acid.

Methods of Manufacturing Antisense Molecules

The antisense molecules used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). One method for synthesising oligonucleotides on a modified solid support is described in U.S. Pat. No. 4,458,066.

Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates—and alkylated derivatives. In one such automated embodiment, diethyl-phosphoramidites are used as starting materials and may be synthesized as described by Beaucage, et al., (1981) Tetrahedron Letters, 22:1859-1862.

The antisense molecules of the invention are synthesised in vitro and do not include antisense compositions of biological origin, or genetic vector constructs designed to direct the in vivo synthesis of antisense molecules. The molecules of the invention may also be mixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption.

5 Therapeutic Agents

The present invention also can be used as a prophylactic or therapeutic, which may be utilised for the purpose of treatment of a genetic disease.

Accordingly, in one embodiment the present invention provides antisense molecules that bind to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping described herein in a therapeutically effective amount admixed with a pharmaceutically acceptable carrier, diluent, or excipient.

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic or similarly untoward reaction, such as gastric upset and the like, when administered to a patient. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in Martin, Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, Pa., (1990).

In a more specific form of the invention there are provided pharmaceutical compositions comprising therapeutically effective amounts of an antisense molecule together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength and additives such as detergents and solubilizing agents (e.g.,

Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol). The material may be incorporated into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hylauronic acid may also be used. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Martin, Remington's Pharmaceutical Sciences, 18th 10 Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 1435-1712 that are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilised form.

It will be appreciated that pharmaceutical compositions 15 provided according to the present invention may be administered by any means known in the art. Preferably, the pharmaceutical compositions for administration are administered by injection, orally, or by the pulmonary, or nasal route. The antisense molecules are more preferably delivered by intravenous, intra-arterial, intraperitoneal, intramuscular, or subcutaneous routes of administration.

Antisense Molecule Based Therapy

Also addressed by the present invention is the use of antisense molecules of the present invention, for manufac- 25 ture of a medicament for modulation of a genetic disease.

The delivery of a therapeutically useful amount of antisense molecules may be achieved by methods previously published. For example, intracellular delivery of the antisense molecule may be via a composition comprising an 30 admixture of the antisense molecule and an effective amount of a block copolymer. An example of this method is described in US patent application US 20040248833.

Other methods of delivery of antisense molecules to the nucleus are described in Mann C J et al., (2001) ["Antisense-35 induced exon skipping and the synthesis of dystrophin in the mdx mouse". Proc., Natl. Acad. Science, 98(1) 42-47J and in Gebski et al., (2003). Human Molecular Genetics, 12(15): 1801-1811.

A method for introducing a nucleic acid molecule into a 40 cell by way of an expression vector either as naked DNA or complexed to lipid carriers, is described in U.S. Pat. No. 6.806.084.

It may be desirable to deliver the antisense molecule in a colloidal dispersion system. Colloidal dispersion systems 45 include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-inwater emulsions, micelles, mixed micelles, and liposomes or liposome formulations.

Liposomes are artificial membrane vesicles which are so useful as delivery vehicles in vitro and in vivo. These formulations may have net cationic, anionic or neutral charge characteristics and are useful characteristics with in vitro, in vivo and ex vivo delivery methods. It has been shown that large unilamellar vesicles (LUV), which range in size from 0.2-4.0.PHI.m can encapsulate a substantial percentage of an aqueous buffer containing large macromolecules. RNA, and DNA can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, et al., Trends Biochem. Sci., 6:77, 60 1981).

In order for a liposome to be an efficient gene transfer vehicle, the following characteristics should be present: (1) encapsulation of the antisense molecule of interest at high efficiency while not compromising their biological activity; 65 (2) preferential and substantial binding to a target cell in comparison to non-target cells; (3) delivery of the aqueous

contents of the vesicle to the target cell cytoplasm at high efficiency; and (4) accurate and effective expression of genetic information (Mannino, et al., Biotechniques, 6:682, 1988)

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The composition of the liposome is usually a combination of phospholipids, particularly high-phase-transition-temperature phospholipids, usually in combination with steroids, especially cholesterol. Other phospholipids or other lipids may also be used. The physical characteristics of liposomes depend on pH, ionic strength, and the presence of divalent cations.

Alternatively, the antisense construct may be combined with other pharmaceutically acceptable carriers or diluents to produce a pharmaceutical composition. Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. The composition may be formulated for parenteral, intramuscular, intravenous, subcutaneous, intraocular, oral or transdermal administration.

The routes of administration described are intended only as a guide since a skilled practitioner will be able to determine readily the optimum route of administration and any dosage for any particular animal and condition. Multiple approaches for introducing functional new genetic material into cells, both in vitro and in vivo have been attempted (Friedmann (1989) Science, 244:1275-1280).

These approaches include integration of the gene to be expressed into modified retroviruses (Friedmann (1989) supra; Rosenberg (1991) Cancer Research 51(18), suppl.: 5074S-5079S); integration into non-retrovirus vectors (Rosenfeld, et al. (1992) Cell, 68:143-155; Rosenfeld, et al. (1991) Science, 252:431-434); or delivery of a transgene linked to a heterologous promoter-enhancer element via liposomes (Friedmann (1989), supra; Brigham, et al. (1989) Am. J. Med. Sci., 298:278-281; Nabel, et al. (1990) Science, 249:1285-1288; Hazinski, et al. (1991) Am. J. Resp. Cell Molec. Biol., 4:206-209; and Wang and Huang (1987) Proc. Natl. Acad. Sci. (USA), 84:7851-7855); coupled to ligandspecific, cation-based transport systems (Wu and Wu (1988) J. Biol. Chem., 263:14621-14624) or the use of naked DNA. expression vectors (Nabel et al. (1990), supra); Wolff et al. (1990) Science, 247:1465-1468). Direct injection of transgenes into tissue produces only localized expression (Rosenfeld (1992) supra); Rosenfeld et al. (1991) supra; Brigham et al. (1989) supra; Nabel (1990) supra; and Hazinski et al. (1991) supra). The Brigham et al. group (Am. J. Med. Sci. (1989) 298:278-281 and Clinical Research (1991) 39 (abstract)) have reported in vivo transfection only of lungs of mice following either intravenous or intratracheal administration of a DNA liposome complex. An example of a review article of human gene therapy procedures is: Anderson, Science (1992) 256:808-813.

The antisense molecules of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to prodrugs and pharmaceutically acceptable salts of the compounds of the invention, pharmaceutically acceptable salts of such pro-drugs, and other bioequivalents.

The term "pharmaceutically acceptable salts" refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

For oligonucleotides, preferred examples of pharmaceutically acceptable salts include but are not limited to (a) salts

formed with cations such as sodium, potassium, ammonium, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, malefic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polygiutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine. The pharmaceutical compositions of the present invention may be administered in a number of ways 15 depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including rectal delivery), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, (including by nebulizer, 20 intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intra-arterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Oligonucleotides with at 25 least one 2'-O-methoxyethyl modification are believed to be particularly useful for oral administration.

The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well 30 known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient (s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Kits of the Invention

The invention also provides kits for treatment of a patient with a genetic disease which kit comprises at least an 40 antisense molecule, packaged in a suitable container, together with instructions for its use.

In a preferred embodiment, the kits will contain at least one antisense molecule as shown in Table 1A, or a cocktail of antisense molecules as shown in Table 1B or a "weasel" 45 compound as shown in Table 1C. The kits may also contain peripheral reagents such as buffers, stabilizers, etc.

Those of ordinary skill in the field should appreciate that applications of the above method has wide application for identifying antisense molecules suitable for use in the treatment of many other diseases.

#### EXAMPLES

The following Examples serve to more fully describe the 55 manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these Examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. 60 The references cited herein are expressly incorporated by reference.

Methods of molecular cloning, immunology and protein chemistry, which are not explicitly described in the following examples, are reported in the literature and are known by 65 those skilled in the art. General texts that described conventional molecular biology, microbiology, and recombinant

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DNA techniques within the skill of the art, included, for example: Sambrook et al, Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989): Glover ed., DNA Cloning: A Practical Approach, Volumes I and II, MRL Press, Ltd., Oxford, U. K. (1985); and Ausubel, F., Brent, R., Kingston, R. E., Moore, D. D., Seidman, J. G., Smith, J. A., Struhl, K. Current Protocols in Molecular Biology. Greene Publishing Associates/Wiley Intersciences, New York (2002).

#### Determining Induced Exon Skipping in Human Muscle Cells

Attempts by the inventors to develop a rational approach in antisense molecules design were not completely successful as there did not appear to be a consistent trend that could be applied to all exons. As such, the identification of the most effective and therefore most therapeutic antisense molecules compounds has been the result of empirical studies.

These empirical studies involved the use of computer programs to identify motifs potentially involved in the splicing process. Other computer programs were also used to identify regions of the pre-mRNA which may not have had extensive secondary structure and therefore potential sites for annealing of antisense molecules. Neither of these approaches proved completely reliable in designing antisense oligonucleotides for reliable and efficient induction of exon skipping.

Annealing sites on the human dystrophin pre-mRNA were selected for examination, initially based upon known or predicted motifs or regions involved in splicing. 20Me antisense oligonucleotides were designed to be complementary to the target sequences under investigation and were synthesised on an Expedite 8909 Nucleic Acid Synthesiser. Upon completion of synthesis, the oligonucleotides were cleaved from the support column and de-protected in ammonium hydroxide before being desalted. The quality of the oligonucleotide synthesis was monitored by the intensity of the trityl signals upon each deprotection step during the synthesis as detected in the synthesis log. The concentration of the antisense oligonucleotide was estimated by measuring the absorbance of a diluted aliquot at 260 nm.

Specified amounts of the antisense molecules were then tested for their ability to induce exon skipping in an in vitro assay, as described below.

Briefly, normal primary myoblast cultures were prepared from human muscle biopsies obtained after informed consent. The cells were propagated and allowed to differentiate into myotubes using standard culturing techniques. The cells were then transfected with the antisense oligonucleotides by delivery of the oligonucleotides to the dells as cationic lipoplexes, mixtures of antisense molecules or cationic liposome preparations.

The cells were then allowed to grow for another 24 hours, after which total RNA was extracted and molecular analysis commenced. Reverse transcriptase amplification (RT-PCR) was undertaken to study the targeted regions of the dystrophin pre-mRNA or induced exonic re-arrangements.

For example, in the testing of an antisense molecule for inducing exon 19 skipping the RT-PCR test scanned several exons to detect involvement of any adjacent exons. For example, when inducing skipping of exon 19, RT-PCR was carried out with primers that amplified across exons 17 and 21. Amplifications of even larger products in this area (i.e. exons 13-26) were also carried out to ensure that there was

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minimal amplification bias for the shorter induced skipped transcript. Shorter or exon skipped products tend to be amplified more efficiently and may bias the estimated of the normal and induced transcript.

The sizes of the amplification reaction products were estimated on an agarose gel and compared against appropriate size standards. The final confirmation of identity of these products was carried out by direct DNA sequencing to establish that the correct or expected exon junctions have been maintained.

Once efficient exon skipping had been induced with one antisense molecule, subsequent overlapping antisense molecules may be synthesized and then evaluated in the assay as described above. Our definition of an efficient antisense molecule is one that induces strong and sustained exon skipping at transfection concentrations in the order of 300 15 nM or less.

## Antisense Oligonucleotides Directed at Exon 8

Antisense oligonucleotides directed at exon 8 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. efficient antisense molecules only induced exon skipping at concentrations of 300 nM and above. Therefore, we have shown that targeting of the antisense molecules to motifs involved in the splicing process plays a crucial role in the overall efficacy of that compound.

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Efficacy refers to the ability to induce consistent skipping of a target exon. However, sometimes skipping of the target exons is consistently associated with a flanking exon. That is, we have found that the splicing of some exons is tightly linked. For example, in targeting exon 23 in the mouse model of muscular dystrophy with antisense molecules directed at the donor site of that exon, dystrophin transcripts missing exons 22 and 23 are frequently detected. As another example, when using an antisense molecule directed to exon 8 of the human dystrophin gene, all induced transcripts are missing both exons 8 and 9. Dystrophin transcripts missing 20 only exon 8 are not observed.

Table 2 below discloses antisense molecule sequences that induce exon 8 (and 9) skipping.

#### TABLE 2

| SEQ | Antisense<br>Oligonucleotide<br>IDname | Sequence                                | Ability to induce skipping        |
|-----|--|---|-----------------------------------|
| 1   | H8A(-06+18)                            | 5'-GAU AGG UGG UAU CAA<br>CAU CUG UAA   | Very strong to 20 nM              |
| 2   | HBA (-03+18)                           | 5'-GAU AGG UGG UAU CAA<br>CAU CUG       | Very strong<br>skipping to 40 nM  |
| 3   | H8A(-07+18)                            | 5'-GAU AGG UGG UAU CAA<br>CAU CUG UAA G | Strong skipping to 40 nM          |
| 4   | H8A(-06+14)                            | 5'-GGU GGU AUC AAC AUC<br>UGU AA        | Skipping to<br>300 nM             |
| 5   | H8A(-10+10)                            | 5'-GUA UCA ACA UCU GUA<br>AGC AC        | Patchy/weak<br>skipping to 100 nm |

FIG. 3 shows differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. H8A(-06+18) [SEQ ID NO:1], which anneals to the last 6 bases of intron 7 and the first 18 bases of exon 8, induces substantial exon 8 and 9 skipping when delivered into cells at a concentration of 20 nM. The shorter antisense molecule, H8A(-06+14) [SEQ ID NO: 4] was only able to induce exon 8 and 9 skipping at 300 nM, a concentration some 15 fold higher than H8A(-06+18), which is the preferred antisense molecule.

This data shows that some particular antisense molecules induce efficient exon skipping while another antisense molecule, which targets a near-by or overlapping region, can be much less efficient. Titration studies show one compound is able to induce targeted exon skipping at 20 nM while the less

Antisense Oligonucleotides Directed at Exon 7

Antisense oligonucleotides directed at exon 7 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 4 shows the preferred antisense molecule, H7A(+ 45+67) [SEQ ID NO: 6], and another antisense molecule, H7A(+2+26) [SEQ ID NO: 7], inducing exon 7 skipping. Nested amplification products span exons 3 to 9. Additional products above the induced transcript missing exon 7 arise from amplification from carry-over outer primers from the RT-PCR as well as heteroduplex formation.

Table 3 below discloses antisense molecule sequences for induced exon 7 skipping.

TABLE 3

| Antisense<br>SEQOligonucleotide<br>ID name | Sequence                       | Ability to induce skipping  |
|--|--------------------------------|-----------------------------|
| 6 H7A(+45+67)                              | 5'-UGC AUG UUC CAG UCG UUG UGU | Strong skipping<br>to 20 nM |

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TABLE 3-continued

| Antisense<br>SEQOligonucleotide<br>ID name | Sequence           |        |     |     |     |     | Ability to ind          | luce |
|--|--------------------|--------|-----|-----|-----|-----|-------------------------|------|
| 7 H7A(+02+26)                              | 5'-CAC U.          | AU UCC | AGU | CAA | AUA | GGU | Weak skipping<br>100 nM | at   |
| 8 H7D(+15-10)                              | 5'-AUU U.<br>AGU A | AC CAA | ccu | UCA | GGA | UCG | Weak skipping<br>300 nM | to   |
| 9 H7A(-18+03)                              | 5'-GGC C           | UA AAA | CAC | AUA | CAC | AUA | Weak skipping           | to   |

## Antisense Oligonucleotides Directed at Exon 6

Antisense oligonucleotides directed at exon 6 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 5 shows an example of two non-preferred antisense molecules inducing very low levels of exon 6 skipping in cultured human cells. Targeting this exon for specific removal was first undertaken during a study of the canine model using the oligonucleotides as listed in Table 4, below.

Some of the human specific oligonucleotides were also evaluated, as shown in FIG. 5. In this example, both antisense molecules target the donor splice site and only induced low levels of exon 6 skipping. Both H6D(+4-21) [SEQ ID NO: 17] and H6D(+18-4) [SEQ ID NO: 18] would be regarded as non-preferred antisense molecules.

One antisense oligonucleotide that induced very efficient exon 6 skipping in the canine model, C6A(+69+91) [SEQ ID NO: 14], would anneal perfectly to the corresponding region in human dystrophin exon 6. This compound was evaluated, found to be highly efficient at inducing skipping of that target exon, as shown in FIG. 6 and is regarded as the preferred compound for induced exon 6 skipping. Table 4 below discloses antisense molecule sequences for induced exon 6 skipping.

#### Antisense Oligonucleotides Directed at Exon 4

Antisense oligonucleotides directed at exon 4 were prepared and tested for their ability to induce exon skipping in 20 human muscle cells using similar methods as described above.

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FIG. 7 shows an example of a preferred antisense molecule inducing skipping of exon 4 skipping in cultured human cells. In this example, one preferred antisense compound, H4A(+13+32) [SEQ ID NO:19], which targeted a presumed exonic splicing enhancer induced efficient exon skipping at a concentration of 20 nM while other non-preferred antisense oligonucleotides failed to induce even low levels of exon 4 skipping. Another preferred antisense molecule inducing skipping of exon 4 was H4A(+111+40) [SEQ ID NO:22], which induced efficient exon skipping at a concentration of 20 nM.

Table 5 below discloses antisense molecule sequences for inducing exon 4 skipping.

TABLE 4

| SEQ I | Antisense Oligo<br>Dname | Ability to induce skipping  |
|-------|--------------------------|---|
| 10    | C6A(-10+10)              | 5' CAU UUU UGA CCU ACA UGU No skipping<br>GG                        |
| 11    | C6A(-14+06)              | 5' UUU GAC CUA CAU GUG GAA No akipping                              |
| 12    | C6A(-14+12)              | 5' UAC AUU UUU GAC CUA CAU No skipping<br>GUG GAA AG                |
| 13    | C6A(-13+09)              | 5' AUU UUU GAC CUA CAU GGG No skipping AAA G                        |
| 14    | CH6A(+69+91)             | 5. UAC GAG UUG AUU GUC GGA Strong skipping to 20 nM $_{\rm CCC}$ AG |
| 15    | C6D (+12-13)             | 5' GUG GUC UCC UUA CCU AUG Weak skipping at 300 nM.<br>ACU GUG G    |
| 16    | C6D(+06-11)              | 5' GGU CUC CUU ACC UAU GA No skipping                               |
| 17    | H6D(+04-21)              | 5) UGU CUC AGU AAU CUU CUU Weak skipping to 50 nM ACC UAU           |
| 18    | H6D(+18-04)              | 5' UCU UAC CUA UGA CUA UGG Very weak skipping to<br>AUG AGA 300 nM  |

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TABLE 5

| SEQAntisense<br>ID Oligonucleotide name | Se        | quen         | ce  |     |     |     |     |         | Ability to<br>induce<br>skipping |
|---|-----------|--------------|-----|-----|-----|-----|-----|---------|----------------------------------|
| 19 H4A(+13+32)                          | 51        | GCA          | UGA | ACU | cuu | GUG | GAU | cc      | Skipping to                      |
| 22 H4A(+11+40)                          | 5 '<br>AU | UGU<br>C CUT | UCA | GGG | CAU | GAA | CUC | UUG UGG | Skipping to                      |
| 20 H4D(+04-16)                          | 51        | CCA          | GGG | UAC | UAC | UUA | CAU | UA      | No skipping                      |
| 21 H4D (+24-44)                         | 5'        | AUC          | GUG | UGU | CAC | AGC | AUC | CAG     | No skipping                      |

Antisense Oligonucleotides Directed at Exon 3

Antisense oligonucleotides directed at exon 3 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H3A(+30+60) [SEQ ID NO:23] induced substantial exon 3 skipping when delivered into cells at a concentration of 20 nM to 600 nM. The antisense molecule, H3A(+35+65) [SEQ ID NO: 24] induced exon skipping at 300 nM.

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Table 6 below discloses antisense molecule sequences that induce exon 3 skipping.

TABLE 6

| SEQ I | Antisense<br>IDOligonucleotide name | Seq       | uenc       | e   |     | Ability to<br>induce<br>skipping |      |       |     |   |   |
|-------|-------------------------------------|-----------|------------|-----|-----|----------------------------------|------|-------|-----|---|---|
| 23    | H3A(+30+60)                         |           | GAG        |     | ccu | ccc                              | AUC  | CUG   | UAG |   | Moderate<br>skipping to<br>20 to 600 nM |
| 24    | H3A(+35+65)                         |           | UCU<br>AGG |     | AGG | CGC                              | CUC  | CCA   | ucc |   | Working to<br>300 nM                    |
| 25    | H3A(+30+54)                         | GCG       | ccu        | CCC | AUC | CUG                              | UAG  | GUC   | ACU | G | Moderate<br>100-600 nM                  |
| 26    | H3D(+46-21)                         | CUU       | CGA        | GGA | GGU | CUA                              | GGA  | GGC   | GCC |   | No skipping                             |
| 27    | H3A(+30+50)                         | cuc       | CCA        | ucc | UGU | AGG                              | UCA  | CUG   |     |   | Moderate 20-600 nt                      |
| 28    | H3D(+19-03)                         | UAC       | CAG        | טטט | UUG | ccc                              | UGU  | CAG   | G   |   | No skipping                             |
| 29    | H3A (-06+20)                        | UCA<br>AA | AUA        | UGC | UGC | uuco                             | CA . | AAC ( | JGA |   | No skipping                             |
| 30    | H3A(+37+61)                         | CUA       | GGA        | GGC | GCC | UCC                              | CAU  | CCU   | GUA | G | No skipping                             |

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#### Antisense Oligonucleotides Directed at Exon 5

Antisense oligonucleotides directed at exon 5 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H5A(+20+50) [SEQ ID NO:31] induces substantial exon 5 skipping when delivered into cells at a concentration of 100 nM. Table 7 below shows other antisense molecules tot fivi. Table 7 below shows other antisense molecules tested. The majority of these antisense molecules were not as effective at exon skipping as H5A(+20+50). However, H5A(+15+45) [SEQ ID NO: 40] was able to induce exon 5 skipping at 300 nM.

Table 7 below discloses antisense molecule sequences that fallow may 5 skipping.

that induce exon 5 skipping.

TABLE 7

| SEQ | Antisense<br>Oligonucleotide<br>ID name | Sequence                                     | Ability to<br>induce<br>skipping |
|-----|---|--|----------------------------------|
| 31  | L H5A(+20+50)                           | UUA UGA UUU CCA UCU ACG<br>AUG UCA GUA CUU C | Working to                       |

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TABLE 7-continued

| SEQ : | Antisense<br>Oligonucleotide<br>ID name | Seq        | uenc       | Ability to induce skipping |            |          |     |              |
|-------|---|------------|------------|----------------------------|------------|----------|-----|--------------|
| 32    | H5D (+25-05)                            | CUU        | ACC        | UGC                        | CAG        | UGG<br>A | AGG | No skipping  |
| 33    | H5D(+10-15)                             | CAU        | CAG        | GAU<br>G                   | טכט        | UAC      | CUG | Inconsistent |
| 34    | H5A(+10+34)                             | CGA<br>UAU | UGU        | CAG                        | UAC        | uuc      | CAA | Very weak    |
| 35    | H5D(-04-21)                             | ACC        | AUU        | CAU                        | CAG        | GAU      | UCU | No skipping  |
| 3.6   | H5D (+16-02)                            | ACC        | UGC        | CAG                        | UGG        | AGG      | AUU | No skipping  |
| 37    | H5A(-07+20)                             | CCA        | AUA<br>UGU | UUC                        | ACU        | AAA      | UCA | No skipping  |
| 38    | H5D(+18-12)                             | CAG<br>GUG | GAU<br>GAG | UCU                        | UAC        | CUG      | CCA | No skipping  |
| 39    | H5A(+05+35)                             | ACG<br>AUA | AUG<br>UUC | UCA<br>ACU                 | GUA<br>AAA | cuu      | CCA | No skipping  |
| 40    | H5A(+15+45)                             | AUU<br>AGU |            |                            | UAC        |          | GUC | Working to   |

Antisense Oligonucleotides Directed at Exon 10

Antisense oligonucleotides directed at exon 10 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H10A(-05+16) [SEQ ID NO:41] induced substantial exon 10 skipping when delivered into cells. Table 8 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was variable. Table 8 below discloses antisense molecule sequences that induce exon 10 skipping.

TABLE 8

| SEQAntisense<br>ID Oligonucleotide name | Seg   | uenc | e   |     |     |     |       | Ability to<br>induce skipping |          |  |
|---|-------|------|-----|-----|-----|-----|-------|-------------------------------|----------|--|
| 41 H10A(-05+16)                         | CAG   | GAG  | CUU | CCA | AAU | GCU | GCA   | Not                           | tested   |  |
| 42 H10A(-05+24)                         | 10000 | GUC  |     | AGG | AGC | UUC | CAA   | Not                           | tested   |  |
| 43 H10A(+98+119)                        | UCC   | UCA  | GCA | GAA | AGA | AGC | CAC G | Not                           | tested   |  |
| 44 H10A(+130+149)                       | UUA   | GAA  | AUC | UCU | CCU | UGU | GC    | No                            | skipping |  |
| 45 H10A(-33-14)                         | UAA   | AUU  | GGG | UGU | UAC | ACA | AU    | No                            | skipping |  |

Antisense Oligonucleotides Directed at Exon 11

Antisense oligonucleotides directed at exon 11 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 8B shows an example of H11A(+75+97) [SEQ ID NO:49] antisense molecule inducing exon 11 skipping in cultured human cells. H11A(+75+97) induced substantial exon 11 skipping when delivered into cells at a concentration of 5 nM. Table 9 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was observed at 100 nM.

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| SEQAntisense<br>ID Oligonucleotide name | Sequ       | (back |     |     |     |     |       | Ability          | to  |      | _  |
|---|------------|-------|-----|-----|-----|-----|-------|------------------|-----|------|----|
|   | sequ       | telle | 9   |     |     |     |       | induce s         | kip | ping |    |
| 46 H11D(+26+49)                         | CCC        | UGA   | GGC | AUU | ccc | AUC | UUG   | Skipping         | at  | 100  | nM |
| 47 H11D(+11-09)                         | AGG        | ACU   | UAC | UUG | cuu | UGU | טט    | Skipping         | at  | 100  | nM |
| 48 H11A(+118+140)                       | CUU        | GAA   | טטט | AGG | AGA | uuc | AUC U |                  |     |      |    |
| 49 H11A(+75+97)                         | CAU        | cuu   | CUG | AUA | AUU | UUC | cug u | U Skipping       | at  | 100  | nM |
| 46 H11D(+26+49)                         | CCC<br>AAU | UGA   | GGC | AUU | ccc | AUC | UUG   | Skipping<br>5 nM | at  |      |    |

## Antisense Oligonucleotides Directed at Exon 12

Antisense oligonucleotides directed at exon 12 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

H12A(+52+75) [SEQ ID NO:50] induced substantial exon 12 skipping when delivered into cells at a concentration of 5 nM, as shown in FIG. 8A. Table 10 below shows other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The antisense molecules ability to induce exon skipping was variable.

TABLE 10

| SEQ<br>ID | Antisense<br>Oligonucleotide<br>name | Seq | uenc | ė   |     | Ability to<br>induce<br>skipping |
|-----------|--------------------------------------|-----|------|-----|-----|----------------------------------|
| 50        | H12A(+52+75)                         | UCU | UCU  | GUU | עטט | Skipping                         |
|           |                                      | GUU | AGC  | CAG | UCA | at 5 nM                          |
| 51        | H12A(-10+10)                         | UCU | AUG  | UAA | ACU | Skipping at                      |
|           |                                      | GAA | AAU  | nn  |     | 100 nM                           |
| 52        | H12A(+11+30)                         | UUC | UGG  | AGA | UCC | No skipping                      |
|           |                                      | AUU | AAA  | AC  |     | S                                |

#### Antisense Oligonucleotides Directed at Exon 13

Antisense oligonucleotides directed at exon 13 were pre- 45 pared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

H13A(+77+100) [SEQ ID NO:53] induced substantial exon 13 skipping when delivered into cells at a concentra- 50 tion of 5 nM. Table 11 below includes two other antisense

molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These other antisense molecules were unable to induce exon skipping.

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TABLE 11

| SEQ I | Antisense<br>Oligonucleotide<br>Dname | Seq | uenc | e   |     | in  | ility to<br>duce<br>ipping |
|-------|---------------------------------------|-----|------|-----|-----|-----|----------------------------|
| 53    | H13A(+77+100)                         | CAG | CAG  | UUG | CGU | sk. | ipping at                  |
|       |                                       | GAU | CUC  | CAC | UAG | 5 1 | Mn                         |
| 54    | H13A (+55+75)                         | UUC | AUC  | AAC | UAC | No  | skipping                   |
|       |                                       | CAC | CAC  | CAU |     |     |                            |
| 55    | H13D(+06-19)                          | CUA | AGC  | AAA | AUA | No  | skipping                   |
|       |                                       |     | UGA  |     |     |     |                            |
|       |                                       | G   |      |     |     |     |                            |

Antisense Oligonucleotides Directed at Exon 14

Antisense oligonucleotides directed at exon 14 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

H14A(+37+64) [SEQ ID NO:56] induced weak exon 14 skipping when delivered into cells at a concentration of 100 nM. Table 12 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

TABLE 12

| SEQ ID | Antisense<br>Oligonucleotide<br>name | Seq        | uenc      | e e        |     |     |     | Ability to<br>induce<br>skipping |
|--------|--------------------------------------|------------|-----------|------------|-----|-----|-----|----------------------------------|
| 56     | H14A(+37+64)                         | CUU        |           | AAA<br>CUG |     | ccc | AGC | Skipping at                      |
| 57     | H14A(+14+35)                         | CAU        | 77700     | CAG        | AUG | טטט | GCC | No skipping                      |
| 58     | H14A(+51+73)                         | GAA<br>GAA | GGA<br>CC | UGU        | CUU | GUA | AAA | No skipping                      |

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SEQ ID name

H14A(-12+12)

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TABLE 12-continued Antisense Oligonucleotide Ability to induce Sequence skipping H14D(-02+18) ACC UGU UCU UCA GUA AGA No skipping H14D(+14-10) CAU GAC ACA CCU GUU CUU No skipping H14A(+61 +80) CAU UUG AGA AGG AUG UCU No skipping

AUC UCC CAA UAC CUG GAG No skipping

## Antisense Oligonucleotides Directed at Exon 15

AAG AGA

Antisense oligonucleotides directed at exon 15 were prepared and tested for their ability to induce exon skipping in 20 human muscle cells using similar methods as described above.

H15A(-12+19) [SEQ ID NO:63] and H15A(+48+71) [SEQ ID NO:64] induced substantial exon 15 skipping when delivered into cells at a concentration of 10 Nm, as shown in FIG. 9A. Table 13 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 Nm. These other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

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#### TABLE 13

| SEQ I | Antisense<br>Oligonucleotide<br>Dname | Seq        | uenc     | e   |     |     |     |     |     |     | in      | ility to<br>duce<br>ipping |
|-------|---------------------------------------|------------|----------|-----|-----|-----|-----|-----|-----|-----|---------|----------------------------|
| 63    | H15A(-12+19)                          | GCC        | AUG<br>U | CAC | UAA | AAA | GGC | ACU | GCA | AGA | sk<br>5 | ipping a                   |
| 64    | H15A(+48+71)                          | ucu        | UUA      | AAG | CCA | GUU | GUG | UGA | AUC |     | Sk<br>5 | ipping a                   |
| 65    | H15A(+08+28)                          | טטט        | CUG      | AAA | GCC | AUG | CAC | UAA |     |     | No      | skippin                    |
| 63    | H15A(-12+19)                          | GCC<br>CAU |          | CAC | UAA | AAA | GGC | ACU | GCA | ĀĢĀ | No      | skippin                    |
| 66    | H15D(+17-08)                          | GUA        | CAU      | ACG | GCC | AGU | טטט | UGA | AGA | C   | No      | skippin                    |

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### Antisense Oligonucleotides Directed at Exon 16

Antisense oligonucleotides directed at exon 16 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above

H16A(-12+19) [SEQ ID NO:67] and H16A(-06+25) [SEQ ID NO:68] induced substantial exon 16 skipping when delivered into cells at a concentration of 10 nM, as shown in FIG. 9B. Table 14 below includes other antisense molecules tested. H16A(-06+19) [SEQ ID NO:69] and H16A(+87+ 109) [SEQ ID NO:70] were tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These two antisense molecules were able to induce exon skipping at 25 nM and 100 nM, respectively. Additional antisense molecules were tested at 100, 200 and 300 nM and did not result in any exon skipping.

#### TABLE 14

| SEQ<br>ID | Antisense<br>Oligonucleotide<br>name | Sequence                        | Ability to<br>induce<br>skipping |
|-----------|--------------------------------------|---------------------------------|----------------------------------|
| 67        | H16A(-12+19)                         | CUA GAU CCG CUU UUA AAA CCU GUU | Skipping at                      |
|           |                                      | AAA ACA A                       | 5 nM                             |

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TABLE 14-continued

| SEQ | Antisense<br>Oligonucleotide<br>name | Sequence                           | Ability to induce skipping |
|-----|--------------------------------------|------------------------------------|----------------------------|
| 69  | H16A(-06+25)                         | UCU UUU CUA GAU CCG CUU UUA AAA    | Skipping at                |
| 69  | H16A(-06+19)                         | CUA GAU CCG CUU UUA AAA CCU GUU A  | Skipping at                |
| 70  | H16A(+87+109)                        | CCG UCU UCU GGG UCA CUG ACU UA     | Skipping at                |
| 71  | H16A(-07+19)                         | CUA GAU CCG CUU UUA AAA CCU GUU AA | No skipping                |
| 72  | H16A(-07+13)                         | CCC CUIT CUIT AND                  | No skipping                |
| 73  | H16A(+12+37)                         | UGG AUU GCU UUU UCU UUU CUA GAU CC |                            |
| 74  | H16A(+92+116)                        | CAU CCU HOS SHE PART               | No skipping                |
| 75. | H16A(+45+67)                         | G AUC UUG UUU GAG UGA AUA CAG U    | No skipping                |
| 76  | H16A(+105+126)                       | GUU AUC CAG CCA UGC UUC CGU C      | No skipping                |
| 7.7 | H16D(+05-20)                         | UGA UAA UUG GUA UCA CUA ACC UGU G  | No skipping                |
| 78  | H16D(+12-11)                         |                                    | No skipping                |

### Antisense Oligonucleotides Directed at Exon 19

Antisense oligonucleotides directed at exon 19 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H19A(+35+65) [SEQ ID NO:79] induced substantial exon 19 skipping when delivered into cells at a concentration of 10 nM. This antisense molecule also showed very strong exon skipping at concentrations of 25, 50, 100, 300 and 600 nM.

FIG. 10 illustrates exon 19 and 20 skipping using a "cocktail" of antisense oligonucleotides, as tested using gel electrophoresis. It is interesting to note that it was not easy to induce exon 20 skipping using single antisense oligonucleotides H20A(+44+71) [SEQ ID NO:81] or H20A(+149+170) [SEQ ID NO:82], as illustrated in sections 2 and 3 of the gel shown in FIG. 10. Whereas, a "cocktail" of antisense oligonucleotides was more efficient as can be seen in section 4 of FIG. 10 using a "cocktail" of antisense oligonucleotides H20A(+44+71) and H20A(+149+170). When the cocktail was used to target exon 19, skipping was even stronger (see section 5, FIG. 10).

FIG. 11 illustrates gel electrophoresis results of exon 19/20 skipping using "weasels" The "weasels" were effec-

tive in skipping exons 19 and 20 at concentrations of 25, 50, 100, 300 and 600 nM. A further "weasel" sequence is shown in the last row of Table 3C. This compound should give good results.

#### Antisense Oligonucleotides Directed at Exon 20

Antisense oligonucleotides directed at exon 20 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

None of the antisense oligonucleotides tested induced exon 20 skipping when delivered into cells at a concentration of 10, 25, 50, 300 or 600 nM (see Table 15). Antisense molecules H20A(-11+17) [SEQ ID NO:86] and H20D(+08-20) [SEQ ID NO:87] are yet to be tested.

However, a combination or "cocktail" of H20A(+44+71) [SEQ ID NO: 81] and H20(+149+170) [SEQ ID NO:82] in a ratio of 1:1, exhibited very strong exon skipping at a concentration of 100 nM and 600 nM. Further, a combination of antisense molecules H19A(+35+65) [SEQ ID NO:79], H20A(+44+71) [SEQ ID NO:81] and H20A(+149+170) [SEQ ID NO:82] in a ratio of 2:1:1, induced very strong exon skipping at a concentration ranging from 10 nM to 600 nM.

TABLE 15

| SEQ<br>ID | Antisense<br>Oligonucleotide<br>name | Sequence                                 | Ability to<br>induce<br>skipping |
|-----------|--------------------------------------|--|----------------------------------|
| 81        | H20A(+44+71)                         | CUG GCA GAA UUC GAU CCA CCG GCU<br>GUU C | No<br>skipping                   |
| 82        | H20A(+147+168)                       | CAG CAG UAG UUG UCA UCU GCU C            | No<br>skipping                   |
| 83        | H20A(+185+203)                       | UGA UGG GGU GGU GGG UUG G                | No<br>skipping                   |
| 84        | H20A (-08+17)                        | AUC UGC AUU AAC ACC CUC UAG AAA G        | No<br>skipping                   |

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TABLE 15-continued

| SEQ        | Antisense<br>Oligonucleotide<br>name | Seq        | uenc     | Ability to<br>induce<br>skipping |     |     |     |     |     |                   |
|------------|--------------------------------------|------------|----------|----------------------------------|-----|-----|-----|-----|-----|-------------------|
| 85         | H20A(+30+53)                         | CCG        | GCU      | GUU                              | CAG | UUG | uuc | UGA | GGC | No<br>skipping    |
| 86         | H20A(-11+17)                         | AUC<br>GAA | UGC<br>A | AUU                              | AAC | ACC | CUC | UAG | AAA | Not tested<br>yet |
| 87         | H20D(+08-20)                         | GAA<br>CAA |          | GAA                              | GAG | AUU | cuu | ACC | UUA | Not tested<br>yet |
| 81 &<br>82 | H20A(+44+71) &<br>H20A(+147+168)     | GUU        | C        |                                  |     |     |     | ccg |     | Very strong       |
|            |                                      | CAG        | CAG      | UAG                              | UUG | UCA | UCU | GCU | c   | skipping          |
|            | H19A(+35+65);<br>H20A(+44+71);       | UGC        | AGU      | U7                               |     |     |     | GCA |     | Very strong       |
|            | H20A(+147+168)                       | GUU        | C;       |                                  |     |     |     | CCG |     | avrbbing          |
|            |                                      | CAG        | CAG      | UAG                              | UUG | UCA | UCU | GCU | C   |                   |

### Antisense Oligonucleotides Directed at Exon 21

Antisense oligonucleotides directed at exon 21 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

H21A(+85+108) [SEQ ID NO:92] and H21A(+85+106) [SEQ ID NO:91] induced exon 21 skipping when delivered into cells at a concentration of 50 nM. Table 16 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping

#### TABLE 16

| 3.9 | Antisense<br>Oligonucleotide name | Sequence   |      |     |     |      |     |     |   |        | Ability to induce skipping |      |      |
|-----|-----------------------------------|------------|------|-----|-----|------|-----|-----|---|--------|----------------------------|------|------|
| 90  | H21A(-06+16)                      | GCC        | GGU  | UGA | cuu | CAU  | CCU | GUG | c | Skips  | at                         | 600  | nM   |
| 91  | H21A(+85+106)                     | cug        | CAU  | CCA | GGA | ACA  | UGG | GUC | c | Skips  | at                         | 50   | nM   |
| 92  | H21A(+85+108)                     | GUC<br>UC  | DGC  | AUC | CAG | GAA  | CAU | GGG |   | skips  | at                         | 50   | nM   |
| 93  | H21A(+08+31)                      | GUU<br>UGA | GAA. | GAU | cug | AUA. | GCC | GGU |   | Skips  | fai                        | int1 | y to |
| 94  | H21D(+18-07)                      | UAC        | UUA  | CUG | ucu | GUA  | GCU | cnn |   | No ski | ppi                        | ing  |      |

## Antisense Oligonucleotides Directed at Exon 22

Antisense oligonucleotides directed at exon 22 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 12 illustrates differing efficiencies of two antisense molecules directed at exon 22 acceptor splice site. H22A(+

125+106) [SEQ ID NO:96] and H22A(+80+101) [SEQ IDNO: 98] induce strong exon 22 skipping from 50 nM to 600 nM concentration.

H22A(+125+146) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO:98] induced exon 22 skipping when delivered into cells at a concentration of 50 nM. Table 17 below shows other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed a variable ability to induce exon skipping.

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TABLE 17

| SEQ I | Antisense<br>oligonucleotide<br>D name | Seq       | uenc | e   |     |     |     |     | Ability to induce   |
|-------|--|-----------|------|-----|-----|-----|-----|-----|---------------------|
| 95    | 95 H22A(+22+45)                        |           | UCA  | UGG | ncn | CCU | GAU | AGC | No skipping         |
| 96    | H22A(+125+146)                         | CUG       | CAA  | UUC | ccc | GAG | מכט | CUG | C Skipping to 50 nM |
| 97    | H22A(+47+69)                           | ACU<br>UG | GCU  | GGA | ccc | AUG | UCC | UGA | Skipping to 300 nM  |
| 98    | H22A(+80+101)                          | CUA       | AGU  | UGA | GGU | AUG | GAG | AGU | Skipping to 50 nM   |
| 99    | H22D(+13-11)                           | UAU       | UCA  | CAG | ACC | UGC | AAU | UCC | No skipping         |

## Antisense Oligonucleotides Directed at Exon 23

Antisense oligonucleotides directed at exon 23 were pre- 20 skipping, pared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 18 below shows antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed no ability to induce exon skipping or are yet to be tested.

TABLE 18

| Antisense<br>oligonucleotide<br>SEQ ID name |              | Seq | uenc       | e | Ability to<br>induce<br>skipping |    |          |
|---|--------------|-----|------------|---|----------------------------------|----|----------|
| 100   | H23A(+34+59) |     | GUG<br>UAG |   |                                  | No | skipping |
| 101   | H23A(+18+39) |     | GCC        |   | 1000                             | No | Skipping |
| 102   | H23A(+72+90) |     | AGA<br>CUU |   | CGC                              | No | Skipping |

#### Antisense Oligonucleotides Directed at Exon 24

Antisense oligonucleotides directed at exon 24 were prepared using similar methods as described above. Table 19 below outlines the antisense oligonucleotides directed at exon 24 that are yet to be tested for their ability to induce exon 24 skipping.

TABLE 19

|     | Antisense<br>oligonucleotide<br>name | Seq        | uenc | e          |           | Abili<br>induce<br>skipp: | 55      |    |
|-----|--------------------------------------|------------|------|------------|-----------|---------------------------|---------|----|
| 103 | H24A(+48+70)                         | GGG<br>CCU |      | GCC<br>UCA | AUU<br>GA | Needs                     | testing |    |
| 104 | H24A(-02+22)                         |            |      | GGG<br>GAU |           | Needs                     | testing | 60 |

# Antisense Oligonucleotides Directed at Exon 25

Antisense oligonucleotides directed at exon 25 were prepared using similar methods as described above. Table 20 below shows the antisense oligonucleotides directed at exon 25 that are yet to be tested for their ability to induce exon 25

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TABLE 20

| SEQ | Antisense<br>oligonucleotide<br>name | Sequence                                 | Ability to<br>induce<br>skipping |
|-----|--------------------------------------|--|----------------------------------|
| 105 | H25A(+9+36)                          | CUG GGC UGA AU<br>GUC UGA AUA<br>UCA CUG | U Needs testing                  |
| 106 | H25A(+131+156)                       | CUG UUG GCA CA<br>GUG AUC CCA CU<br>AG   | The second second second         |
| 107 | H25D(+16-08)                         | GUC UAU ACC UG<br>UGG CAC AUG UG         |                                  |

### Antisense Oligonucleotides Directed at Exon 26

Antisense oligonucleotides directed at exon 26 were pre-40 pared using similar methods as described above. Table 21 below outlines the antisense oligonucleotides directed at exon 26 that are yet to be tested for their ability to induce exon 26 skipping.

TABLE 21

| -   | Antisense<br>oligonucleotide<br>name | Ability tinduce skipping                                   |      |  |  |
|-----|--------------------------------------|--|------|--|--|
| 108 | H26A(+132+156)                       | UGC UUU CUG UAA Needs tes<br>UUC AUC UGG AGU<br>U          | ting |  |  |
| 109 | H26A(-07+19)                         | CCU CCU UUC UGG Needs tes<br>CAU AGA CCU UCC<br>AC         | ting |  |  |
| 110 | H26A(+68+92)                         | UGU GUC AUC CAU Faint UCG UGC AUC UCU skipping G at 600 nM |      |  |  |

#### Antisense Oligonucleotides Directed at Exon 27

Antisense oligonucleotides directed at exon 27 were prepared using similar methods as described above. Table 22 below outlines the antisense oligonucleotides directed at exon 27 that are yet to be tested for their ability to induce exon 27 skipping.

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TABLE 22

| SEQ I | Antisense<br>oligonucleotide<br>D name | Seq        | ienc     | e   |     |     |     |     | Ability to induce                         |  |
|-------|--|------------|----------|-----|-----|-----|-----|-----|---|--|
| 111   | H27A(+82+106)                          | UUA<br>GUG | AGG<br>G | ccu | cuu | GUG | CUA | CAG | Needs testing                             |  |
| 112   | H27A(-4+19)                            | GGG<br>GA  | ccu      | CUU | CUU | UAG | cuc | ucu | Faint skipping at                         |  |
| 113   | H27D(+19-03)                           | GAC        | UUC      | CAA | AGU | con | GCA | טטט | C v. strong skipping<br>at 600 and 300 nM |  |

Antisense Oligonucleotides Directed at Exon 28

Antisense oligonucleotides directed at exon 28 were prepared using similar methods as described above. Table 23 below outlines the antisense oligonucleotides directed at exon 28 that are yet to be tested for their ability to induce exon 28 skipping.

TABLE 23

| SEQ I | Antisense<br>oligonucleotide<br>Dname | Seq        | uenc | e   |     | Ability to induce skipping |     |     |   |
|-------|---------------------------------------|------------|------|-----|-----|----------------------------|-----|-----|---|
| 114   | H28A(-05+19)                          | GCC<br>AAG | AAC  | AUG | ccc | AAA                        | cuu | CCU | v, strong skipping<br>at 600 and 300 nM |
| 115   | H28A(+99+124)                         | CAG        |      | טטט | ccu | CAG                        | CUC | CGC | Needs testing                           |
| 116   | H28D(+16-05)                          | CUU        | ACA  | UCU | AGC | ACC                        | UCA | GAG | v. strong skipping<br>at 600 and 300 nM |

Antisense Oligonucleotides Directed at Exon 29

Antisense oligonucleotides directed at exon 29 were prepared using similar methods as described above. Table 24 below outlines the antisense oligonucleotides directed at 40 exon 29 that are yet to be tested for their ability to induce exon 29 skipping.

TABLE 24

| SEQ I | Antisense<br>oligonucleotide<br>SEQ ID name |     | uenc | e   |     | Ability to induce skipping |     |     |   |    |                                   |
|-------|---|-----|------|-----|-----|----------------------------|-----|-----|---|----|-----------------------------------|
| 117   | H29A(+57+81)                                | UCC |      | AUC | UGU | UAG                        | GGU | CUG |   | Ne | eds testing                       |
| 118   | H29A(+18+42)                                | AUU |      | GUU | AUC | CUC                        | UGA | AUG |   |    | strong skipping<br>600 and 300 nM |
| 119   | H29D(+17-05)                                | CAU | ACC  | UCU | UCA | UGU                        | AGU | UCC | C |    | strong skipping<br>600 and 300 nM |

Antisense Oligonucleotides Directed at Exon 30

Antisense oligonucleotides directed at exon 30 were prepared using similar methods as described above. Table 25 below outlines the antisense oligonucleotides directed at exon 30 that are yet to be tested for their ability to induce exon 30 skipping.

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TABLE 25

| Antisense<br>oligonucleotide<br>SEQ ID name |                     |          | Seq         | uenc       | e         |             |     | Ability to induce |  |  |  |  |  |
|---|---------------------|----------|-------------|------------|-----------|-------------|-----|-------------------|--|--|--|--|--|
| 120   | 120 H30A (+122+147) |          | CAU UUG AGC |            |           | UGC GUC CAC |     |                   |  |  |  |  |  |
| 121   | H30A                | (+25+50) | COC         | UGG<br>UGU | GCA<br>UC | GAC         | UGG | AUG               | Very strong skipping at<br>600 and 300 nM. |  |  |  |  |
| 122   | H30D                | (+19-04) | UUG<br>GCA  | nn<br>ccn  | GGG       | CUU         | ccu | GAG               | Very strong skipping at<br>600 and 300 nM. |  |  |  |  |

# Antisense Oligonucleotides Directed at Exon 31

Antisense oligonucleotides directed at exon 31 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 13 illustrates differing efficiencies of two antisense 20 molecules directed at exon 31 acceptor splice site and a

"cocktail" of exon 31 antisense oligonucleotides at varying concentrations. H31D(+03-22) [SEQ ID NO:124] substantially induced exon 31 skipping when delivered into cells at a concentration of 20 nM. Table 26 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 26

| SEQ I |      | sense<br>onucleotide | Seq        | ienc   | e   |     | Ability to induce skipping |     |     |            |          |
|-------|------|----------------------|------------|--------|-----|-----|----------------------------|-----|-----|------------|----------|
| 123   | H31D | (+06-18)             | UUC        | UGA    | AAU | AAC | AUA                        | UAC | CUG | Skipping t | o 300 nM |
| 124   | H31D | (+03-22)             | UAG        | g<br>G | CUG | AAA | UAA                        | CAU | AUA | Skipping t | o 20 nM  |
| 125   | H31A | (+05+25)             | GAC        | UUG    | UCA | AAU | CAG                        | AUU | GGA | No skippir | ig       |
| 126   | H31D | (+04-20)             | GUU<br>UGU | ucu    | GAA | AUA | ACA                        | UAU | ACC | Skipping t | o 300 nM |

#### Antisense Oligonucleotides Directed at Exon 32

- Antisense oligonucleotides directed at exon 32 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.
- H32D(+04-16) [SEQ ID NO:127] and H32A(+49+73)
  45 [SEQ ID NO:130] induced exon 32 skipping when delivered into cells at a concentration of 300 nM. Table 27 below also shows other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules did not show an ability to induce exon skipping.

#### TABLE 27

| Anti:<br>SEQolige<br>ID name | Seq        | uenc      | е        |     | Ability to induce skipping |     |     |     |     |       |     |     |    |
|------------------------------|------------|-----------|----------|-----|----------------------------|-----|-----|-----|-----|-------|-----|-----|----|
| 127H32D                      | (+04-16)   | CAC       | CAG      | AAA | UAC                        | AUA | CCA | CA  | Ski | pping | to  | 300 | nM |
| 128H32A                      | (+151+170) | CAA       | UGA      | טטט | AGC                        | UGU | GAC | UG  | No  | skipp | ing |     |    |
| 129H32A                      | (+10+32)   | CGA<br>UG | AAC      | uuc | AUG                        | GAG | ACA | ucu | No  | skipp | ing |     |    |
| 130H32A                      | (+49+73)   | CUU       | GUA<br>C | GAC | GCU                        | GCU | CAA | AAU | Ski | pping | to  | 300 | nM |

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Antisense Oligonucleotides Directed at Exon 33

Antisense oligonucleotides directed at exon 33 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described 5 above.

FIG. 14 shows differing efficiencies of two antisense molecules directed at exon 33 acceptor splice site. H33A(+64+88) [SEQ ID NO:134] substantially induced exon 33 skipping when delivered into cells at a concentration of 10 nM. Table 28 below includes other antisense molecules tested at a concentration of 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 28

| SEQ |      | sense<br>gonucleotide | Seq        | uenc | e   |     |     |     |     |       | Ability<br>skipping |     | ind | ıce   |
|-----|------|-----------------------|------------|------|-----|-----|-----|-----|-----|-------|---------------------|-----|-----|-------|
| 13  | Н3ЭЕ | (+09-11)              | CAU        | GCA  | CAC | Acc | טטט | GCU | CC  |       | No skipp            | ing |     |       |
| 132 | Н33А | (+53+76)              | nca        | GUA  | CAA | ncn | GAC | GUC | CAG | UCU   | Skipping            | to  | 200 | nMn ( |
| 132 | нзза | (+30+56)              | GUG<br>GAC | טטט  | AUC | ACC | AUU | ucc | ACU | UCA   | Skipping            | to  | 200 | ) nM  |
| 134 | нзза | (+64+88)              | GCG        | ucu  | GCU | טטט | nca | GUA | CAA | UCU G | Skipping            | to  | 10  | nM    |

Antisense Oligonucleotides Directed at Exon 34

Antisense oligonucleotides directed at exon 34 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 29 below includes antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 29

| SEQ I | 12002 | sense<br>onucleotide | Seq        | uenc       | e          |            | Ability to induce skipping |     |                    |
|-------|-------|----------------------|------------|------------|------------|------------|----------------------------|-----|--------------------|
| 135   | H34A  | (+83+104)            | UCC        |            | ucu        | GUA        | GCU                        | GGC | No skipping        |
| 136   | нз4А  | (+143+165)           | CCA        |            | AAC        | UUC        | AGA                        | AUC | No skipping        |
| 137   | H34A  | (-20+10)             |            |            |            | CCU        |                            | AAG | Not tested         |
| 138   | H34A  | (+46+70)             |            | UCA        |            | ccu        | UUC                        | GCA | Skipping to 300 nM |
| 139   | Н34А  | (+95+120)            |            | UCU        |            | UGU        | CAA                        | UUC | Skipping to 300 nM |
| 140   | H34D  | (+10-20)             | UUC<br>ACC | AGU<br>UUU | GAU<br>CCC | AUA<br>CAG | GGU                        | טטט | Not tested         |
| 141   | H34A  | (+72+96)             | CUG<br>CUG |            |            | CCA        | GCC                        | AUU | No skipping        |

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Antisense Oligonucleotides Directed at Exon 35

Antisense oligonucleotides directed at exon 35 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 15 shows differing efficiencies of antisense molecules directed at exon 35 acceptor splice site. H35A(+24+43) [SEQ ID NO:144] substantially induced exon 35 skipping when delivered into cells at a concentration of 20 nM. Table 30 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed no ability to induce exon skipping.

#### TABLE 30

| SEQ I |       | sense<br>onucleotide | Seq | uenc | e   |     |     |     |     | Ability to induce skipping |
|-------|-------|----------------------|-----|------|-----|-----|-----|-----|-----|----------------------------|
| 142   | H35A  | (+141+161)           | UCU | ucu  | GCU | CGG | GAG | GUG | ACA | Skipping to 20 nM          |
| 143   | H35A  | (+116+135)           |     |      |     |     |     |     |     | No skipping                |
| 144   | H35A. | (+24+43)             |     |      |     | GCA |     |     |     | No skipping                |

Antisense Oligonucleotides Directed at Exon 36

Antisense oligonucleotides directed at exon 36 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense molecule H36A(+26+50) [SEQ ID NO:145] 30 induced exon 36 skipping when delivered into cells at a concentration of 300 nM, as shown in FIG. 16.

Antisense Oligonucleotides Directed at Exon 37

Antisense oligonucleotides directed at exon 37 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

FIG. 17 shows differing efficiencies of two antisense molecules directed at exon 37 acceptor splice site. H37A(+ 82+105) [SEQ ID NO:148] and H37A(+134+157) [SEQ ID NO:149] substantially induced exon 37 skipping when delivered into cells at a concentration of 10 nM. Table 31 below shows the antisense molecules tested.

#### TABLE 31

| SEQ I |       | sense<br>onucleotide | Seq | uenc | e   |     |     |     |     |       | Ability t | o ind | uce |
|-------|-------|----------------------|-----|------|-----|-----|-----|-----|-----|-------|-----------|-------|-----|
| 147   | H37A  | (+26+50)             | CGU | GUA  | GAG | UCC | ACC | טטט | GGG | CGU A | No skippi | ng    |     |
| 148   | H37A  | (+82+105)            | UAC | UAA  | טטט | ccu | GCA | GUG | GUC | ACC   | Skipping  | to 10 | nM  |
| 149   | H3.7A | (+134+157)           | uuc | UGU  | GUG | AAA | ugg | CUG | CAA | AUC   | Skipping  | to 10 | nM  |

Antisense Oligonucleotides Directed at Exon 38

Antisense oligonucleotides directed at exon 38 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 18 illustrates antisense molecule H38A(+88+112) [SEQ ID NO:152], directed at exon 38 acceptor splice site. H38A(+88+112) substantially induced exon 38 skipping when delivered into cells at a concentration of 10 nM. Table 32 below shows the antisense molecules tested and their ability to induce exon skipping.

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TABLE 32

| Antisense<br>SEQoligonucleotide<br>ID name | Sequ       | lenc     | ė   |     |     |     |     | Ability to induce |
|--|------------|----------|-----|-----|-----|-----|-----|-------------------|
| 150H38A (-01+19)                           | CCU        | UCA      | AAG | GAA | UGG | AGG | cc  | No skipping       |
| 151H38A (+59+83)                           | UGC<br>GGU | UGA<br>U | AUU | UCA | GCC | UCC | AGU | Skipping to 10 nM |
| 152H38A (+88+112)                          | UGA<br>UCA |          | CUU | CCU | cuu | UCA | GAU | Skipping to 10 nM |

Antisense Oligonucleotides Directed at Exon 39

Antisense oligonucleotides directed at exon 39 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H39A(+62+85) [SEQ ID NO:153] induced exon 39 skipping when delivered into cells at a concentration of 100 nM. Table 33 below shows the antisense molecules tested and their ability to induce exon skipping.

TABLE 33

| SEQ I |      | sense<br>onucleotide | Seq | uenc | e   |     |     |     |     | Ability to induce skipping |
|-------|------|----------------------|-----|------|-----|-----|-----|-----|-----|----------------------------|
| 153   | нзэа | (+62+85)             | CUG |      | uuc | ucu | CAU | CUG | UGA | Skipping to 100 nM         |
| 154   | H39A | (+39+58)             | GUU | GUA  | AGU | UGU | cuc | CUC | uu  | No skipping                |
| 155   | H39A | (+102+121)           | UUG | ucu  | GUA | ACA | GCU | GCU | GU  | No skipping                |
| 156   | H39D | (+10-10)             | GCU | CUA  | AUA | CCU | UGA | GAG | CA  | Skipping to 300 nM         |

Antisense Oligonucleotides Directed at Exon 40

Antisense oligonucleotides directed at exon 40 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 19 illustrates antisense molecule H40A(-05+17) 45 [SEQ ID NO:157] directed at exon 40 acceptor splice site. Il40A(-05+17) and H40A(+129+153) [SEQ ID NO:158] both substantially induced exon 40 skipping when delivered into cells at a concentration of 5 nM.

Antisense Oligonucleotides Directed at Exon 42

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Antisense oligonucleotides directed at exon 42 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 20 illustrates antisense molecule H42A(-04+23) [SEQ ID NO:159], directed at exon 42 acceptor splice site. H42A(-4+23) and H42D(+19-02) [SEQ ID NO:161] both induced exon 42 skipping when delivered into cells at a concentration of 5 nM. Table 34 below shows the antisense molecules tested and their ability to induce exon 42 skipping.

TABLE 34

| SEQ I | 200  | sense<br>onucleotide | Sequence                               | Ability to induce skipping |
|-------|------|----------------------|--|----------------------------|
| 159   | H42A | (-4+23)              | AUC GUU UCU UCA CGG ACA GUG<br>UGG UGC | Skipping to 5 nM           |
| 160   | H42A | (+86+109)            | GGG CUU GUG AGA CAU GAG UGA            | Skipping to 100 nM         |
| 161   | H42D | (+19-02)             | A CCU UCA GAG GAC UCC UCU<br>UGC       | Skipping to 5 nM           |

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Antisense Oligonucleotides Directed at Exon 43

Antisense oligonucleotides directed at exon 43 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H43A(+101+120) [SEQ ID NO:163] induced exon 43 skipping when delivered into cells at a concentration of 25 nM. Table 35 below includes the antisense molecules tested and their ability to induce exon 43 skipping.

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Antisense Oligonucleotides Directed at Exon 47
Antisense oligonucleotides directed at exon 47 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

H47A(+76+100) [SEQ ID NO:170] and H47A(-09+12) [SEQ ID NO:172] both induced exon 47 skipping when delivered into cells at a concentration of 200 nM. H47D(+25-02) [SEQ ID NO: 171] is yet to be prepared and tested.

TABLE 35

| SEQ I |      | sense<br>onucleotide | Seq        | uenc     | e   |     |     |     |        | Ability to induce skipping |
|-------|------|----------------------|------------|----------|-----|-----|-----|-----|--------|----------------------------|
| 162   | H43D | (+10-15)             | UAU<br>GGU | GUG<br>C | UUA | ccu | ACC | cuu | GUC    | Skipping to 100 nM         |
| 163   | H43A | (+101+120)           | GGA        | GAG      | AGC | UUC | CUG | UAG | CU     | Skipping to 25 nM          |
| 164   | H43A | (+78+100)            | UCA        | ccc      | טטט | CCA | CAG | GCG | UUG CA | Skipping to 200 nM         |

## Antisense Oligonucleotides Directed at Exon 44

Antisense oligonucleotides directed at exon 44 were prepared using similar methods as described above. Testing for the ability of these antisense molecules to induce exon 44 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 165 to 167 in Table 1A.

## Antisense Oligonucleotides Directed at Exon 45

Antisense oligonucleotides directed at exon 45 were prepared using similar methods as described above. Testing for the ability of these antisense molecules to induce exon 45 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 207 to 211 in Table 1A.

#### Antisense Oligonucleotides Directed at Exon 46

Antisense oligonucleotides directed at exon 46 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 21 illustrates the efficiency of one antisense molecule directed at exon 46 acceptor splice site. Antisense oligonucleotide H46A(+86+115) [SEQ ID NO:203] showed very strong ability to induce exon 46 skipping. Table 36 below includes antisense molecules tested. These antisense molecules showed varying ability to induce exon 46 skipping.

### Antisense Oligonucleotides Directed at Exon 50

Antisense oligonucleotides directed at exon 50 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense oligonucleotide molecule H50A(+02+30) [SEQ ID NO: 173] was a strong inducer of exon skipping. Further, H50A(+07+33) [SEQ ID NO:174] and H50D(+07-18) [SEQ ID NO:175] both induced exon 50 skipping when delivered into cells at a concentration of 100 nM.

#### Antisense Oligonucleotides Directed at Exon 51

Antisense oligonucleotides directed at exon 51 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 22 illustrates differing efficiencies of two antisense molecules directed at exon 51 acceptor splice site. Antisense oligonucleotide H51A(+66+90) [SEQ ID NO:180] showed the stronger ability to induce exon 51 skipping. Table 37 below includes antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 51 skipping. The strongest inducers of exon skipping were antisense oligonucleotide H51A(+61+90) [SEQ ID NO: 179] and H51A(+66+95) [SEQ ID NO: 181].

TABLE 36

| SEQ I |      | sense<br>onucleotide | Seq        | uenc       | e   |     |     |     |     |     | Abil<br>indu<br>skip | 7                 |
|-------|------|----------------------|------------|------------|-----|-----|-----|-----|-----|-----|----------------------|-------------------|
| 168   | H46D | (+16-04)             | UUA        | CCU        | UGA | CUU | GCU | CAA | GC  |     | No s                 | kipping           |
| 169   | H46A | (+90+109)            | UCC        | AGG        | טטכ | AAG | UGG | GAU | AC  |     | No s                 | kipping           |
| 203   | H46A | (+86+115)            | 0.00       |            | ucc | AGG | uuc | AAG | UGG | GAU |                      | skipping<br>00 nM |
| 204   | H46A | (+107+137)           | CAA        | GCU        |     | cuu | UUA | GUU | GCU | GCU |                      | skipping<br>od nM |
| 205   | H46A | (-10+20)             | UAU<br>AGA | UCU<br>AAG | טטט | GUU | cuu | CUA | GCC | UGG | Weak                 | skipping          |
| 206   | H46A | (+50+77)             |            | cuu        | ccu | CCA | ACC | AUA | AAA | CAA | Weak                 | skipping          |

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TABLE 37

| SEQ I | Antisense<br>oligonucleotide<br>SEQ ID name |                    |            | uenc              | e          |            |            | Alt      | Ability to induce skipping |  |  |
|-------|---|--------------------|------------|-------------------|------------|------------|------------|----------|----------------------------|--|--|
| 176   | H51A  | (-01+25)           | ACC        | AGA               | GUA        | ACA<br>GC  | GUC        | _        | int skipping               |  |  |
| 177   | H51D  | (+16-07)           | CUC        | AUA               | CCU        | UÇU        | GCU        | Sk       | ipping at 300 nM           |  |  |
| 178   | H51A  | (+111+134)         | UUC        | UGU               | CCA        | AGC        | ccg        | Ne       | eds re-testing             |  |  |
| 179   | H51A  | (+61+90)           | ACA<br>GCA | UCA               | AGG        | AAG        | AUG        | Ve<br>sk | ry strong<br>ipping        |  |  |
| 180   | H51A  | (+66+90)           | ACA<br>GCA | UCA               | AGG<br>CUA | AAG<br>G   | AUG        | sk       | ipping                     |  |  |
| 181   | H51A  | (+66+95)           | CUC<br>AGA | CAA               | CAU        | CAA        | GGA<br>UAG | Ve<br>sk | ry strong<br>ipping        |  |  |
| 182   | H51D  | (+08-17)           | AUC<br>ACC | AUU               | UUU<br>UGC | UCU        | CAU        | No       | skipping                   |  |  |
| 183   | H51A/                                       | D (+08-17)<br>5+?) | ACC        | AUU<br>UUC<br>AAA | UGC        | UCU<br>UAG | CAU        | No       | skipping                   |  |  |
| 184   | H51A  | (+175+195)         | CAC        | CCA<br>GUG        | CCA        | UCA        | GCC        | No       | skipping                   |  |  |
| 185   | H51A  | (+199+220)         | AUC        | AUC               | UCG<br>A   | UUG        | AUA        | No       | skipping                   |  |  |

Antisense Oligonucleotides Directed at Exon 52

Antisense oligonucleotides directed at exon 52 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 22 also shows differing efficiencies of four antisense molecules directed at exon 52 acceptor splice site. The most effective antisense oligonucleotide for inducing exon 52 skipping was H52A(+17+37) [SEQ ID NO:188).

Table 38 below shows antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These 45 antisense molecules showed varying ability to induce exon 50 skipping. Antisense molecules H52A(+12+41) [SEQ ID NO:187] and H52A(+17+37) [SEQ ID NO:188] showed the strongest exon 50 skipping at a concentration of 50 nM.

Antisense Oligonucleotides Directed at Exon 53

Antisense oligonucleotides directed at exon 53 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 22 also shows antisense molecule H53A(+39+69) [SEQ ID NO:193] directed at exon 53 acceptor splice site.

This antisense oligonucleotide was able to induce exon 53 skipping at 5, 100, 300 and 600 nM. A "cocktail" of three exon 53 antisense oligonucleotides: H53A(+23+47) [SEQ ID NO:195], H53A(+150+176) [SEQ ID NO:196] and H53D(+14-07) [SEQ ID NO:194], was also tested, as shown in FIG. 20 and exhibited an ability to induce exon skipping.

Table 39 below includes other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 53 skipping. Antisense molecule H53A(+39+69) [SEQ ID NO:193] induced the strongest exon 53 skipping.

TABLE 38

|         | sense<br>onucleotide | Seq | uenc | e   |     |     |     |         | Ability to<br>induce skipping |  |  |
|---------|----------------------|-----|------|-----|-----|-----|-----|---------|-------------------------------|--|--|
| 186H52A | (-07+14)             | ucc | UGC  | AUU | GUU | GCC | UGU | AAG     | No skipping                   |  |  |
| 187H52A | (+12+41)             |     | AAC  | UGG | GGA | CGC | CUC | ngu nco | Very strong<br>skipping       |  |  |
| 188H52A | (+17+37)             | ACU | GGG  | GAC | GCC | UCU | GUU | CCA     | Skipping to<br>50 nM          |  |  |
| 189H52A | (+93+112)            | CCG | UAA  | UGA | UUG | uuc | UAG | CC      | No skipping                   |  |  |
| 190H52D | (+05-15)             | UGU | UAA  | AAA | ACU | UAC | UUC | GA      | No skipping                   |  |  |

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TABLE 39

| SEQ : |      | isense<br>gonucleotide<br>e |            | Jueno      | e        |          |          |     | Ability to induce               |
|-------|------|-----------------------------|------------|------------|----------|----------|----------|-----|---------------------------------|
| 191   | H53A | 4 (+45+69)                  | CAU        | UCA        | ACU<br>G | GUU      | GCC      | UCC |                                 |
| 192   | H53A | (+39+62)                    | CUG        | GUG        | ccu      | CCG      | GUU      | CUG | Faint skipping at               |
| 193   | H53A | (+39+69)                    | CAU        | UCA        | ACU      | GUU      | GCC<br>G | UCC | Strong skipping                 |
| 194   | H53D | (+14-07)                    | UAC        | UAA        | ccu      | UGG      | טטט      | CUG | Very faint<br>skipping to 50 nM |
| 195   | H53A | (+23+47)                    | CUG        | AAG        | GUG      | uuc<br>c | UUG      |     | Very faint<br>skipping to 50 nM |
| 196   | H53A | (+150+176)                  | UGU        | AUA<br>UGA | GGG      | ACC      | CUC      | cuu |                                 |
| 197   | H53D | (+20-05)                    | CUA<br>AUU | ACC        | UUG      | GUU      | nca      | GUG |                                 |
| 198   | H53D | (+09-18)                    | GGU<br>AAC | AUC        | UUU      | GAU      | ACU      |     | Paint at 600 nM                 |
| 199   | H53A | (-12+10)                    | AUU<br>AUA | CUU<br>AAA | UCA<br>G | ACU      | AGA      |     | No skipping                     |
| 200   | H53A | (-07+18)                    | GAU<br>CAA | UCU<br>CUA |          |          | טטט      |     | No skipping                     |
| 201   | H53A | (+07+26)                    | AUC<br>UC  | CCA        | CUG      | AUU      | CUG      | AAU | No skipping                     |
| 202   | H53A | (+124+145)                  | UUG<br>AAG | GCU<br>A   | CUG      | GCC      | UGU      | ccu | No skipping                     |

#### SEQUENCE LISTING

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95

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106 -continued Human 2'-O-methyl phosphorothioate antisense oligonucleotide <400> SEQUENCE: 110 ugugucaucc auucgugcau cucug 25 <210> SEQ ID NO 111 <211> LENGTH: 25 <212> TYPE: RNA <213 > ORGANISM: Artificial Sequence c220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense <400 > SEQUENCE: 111 uuaaggccuc uugugcuaca ggugg 25 <210> SEQ ID NO 112 <211> LENGTH: 23 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <220 > FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 112 gggccucuuc uuuagcucuc uga 23 <210> SEQ ID NO 113 <211> LENGTH: 22 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 113 gacuuccaaa gucuugcauu uc 22 <210> SEQ ID NO 114 <211> LENGTH: 24 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 114 24 gccaacauge ccaaacuuce uaag <210 > SEQ ID NO 115 <211> LENGTH: 26 <212> TYPE: RNA <213 > ORGANISM: Artificial Sequence <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 115 26 cagagauuuc cucagcuccg ccagga <210 > SEQ ID NO 116

107

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128

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133

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What is claimed is:

1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a 40 morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

 A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping, or a pharmaceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

\* \* \* \* \*

Case 1:21-cv-01015-JLH Document 167-1 Filed 03/20/23 Page 117 of 359 PageID

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

: 9,994,851 B2 PATENT NO. APPLICATION NO. : 15/705172 : June 12, 2018 DATED : Wilton et al. (NVENTOR(S)

Page 1 of 1

is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

Column 1, Line 26, before "STATEMENT REGARDING SEQUENCE LISTING", insert: -STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

This invention was made with government support under grant number R01 NS044146 awarded by the National Institutes of Health. The government has certain rights in the invention.--

> Signed and Sealed this Thirty-first Day of July, 2018

Andrei Iancu

Director of the United States Patent and Trademark Office

# EXHIBIT 2



US010227590B2

## (12) United States Patent

Wilton et al.

(10) Patent No.:

US 10,227,590 B2

(45) Date of Patent:

\*Mar. 12, 2019

## (54) ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

## (71) Applicant: The University of Western Australia, Crawley (AU)

## (72) Inventors: Stephen Donald Wilton, Applecross (AU); Sue Fletcher, Bayswater (AU); Graham McClorey, Bayswater (AU)

#### (73) Assignee: The University of Western Australia, Crawley (AU)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: 16/112,371

(22) Filed: Aug. 24, 2018

#### (65) Prior Publication Data

US 2018/0371458 A1 Dec. 27, 2018

## Related U.S. Application Data

(63) Continuation of application No. 15/274,772, filed on Sep. 23, 2016, which is a continuation of application No. 14/740,097, filed on Jun. 15, 2015, now Pat. No. 9,605,262, which is a continuation of application No. 13/741,150, filed on Jan. 14, 2013, now abandoned, which is a continuation of application No. 13/168.857, filed on Jun. 24, 2011, now abandoned, which is a continuation of application No. 12/837,359, filed on Jul. 15, 2010, now Pat. No. 8,232,384, which is a continuation of application No. 11/570.691. filed as application No. PCT/AU2005/000943 on Jun. 28, 2005, now Pat. No. 7,807,816.

## (30) Foreign Application Priority Data

Jun. 28, 2004 (AU) ...... 2004903474

(51) Int. Cl. C07H 21/04 (2006.01) C12N 15/113 (2010.01)

(52) U.S. Cl.

CPC ....... CI2N 15/113 (2013.01); CI2N 2310/11 (2013.01); CI2N 2310/315 (2013.01); CI2N 2310/321 (2013.01); CI2N 2310/3233 (2013.01); CI2N 2310/33 (2013.01); CI2N 2310/3341 (2013.01); CI2N 2310/3519 (2013.01); CI2N 2320/30 (2013.01); CI2N 2320/33 (2013.01)

(58) Field of Classification Search

None

See application file for complete search history.

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(Continued)

Primary Examiner - Kimberly Chong

(74) Attorney, Agent, or Firm — Sterne, Kessler, Goldstein & Fox P.L.L.C.

#### (57) ABSTRACT

An antisense molecule capable of binding to a selected target site to induce exon skipping in the dystrophin gene, as set forth in SEQ ID NO: 1 to 214.

## 2 Claims, 22 Drawing Sheets

Specification includes a Sequence Listing.

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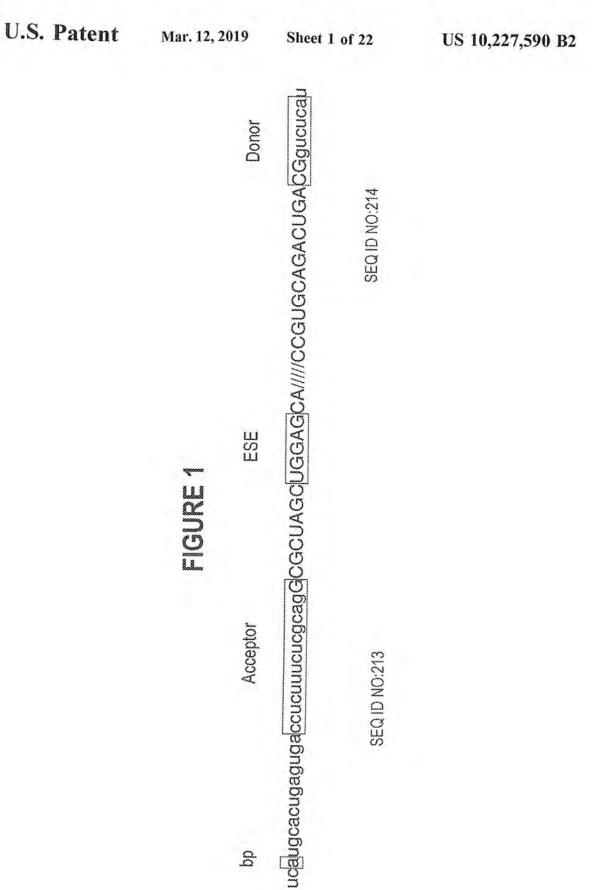
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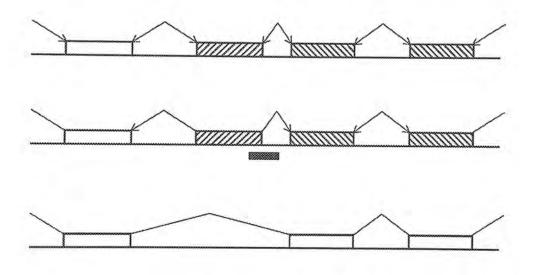


FIGURE 2

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FIGURE 3

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H7A(+45+67) H7A(+2+26)
M 600 300 100 50 20 600NM 600 300 100 50 20 600N M

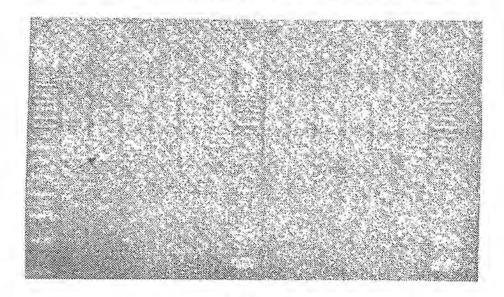


FIGURE 4

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H6D(+4-21) H6D(+18+4)

(nM)

M 600 300 100 50 20 600N M 600 300 100 50 20 UT

FIGURE 5

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6A(+69+91)

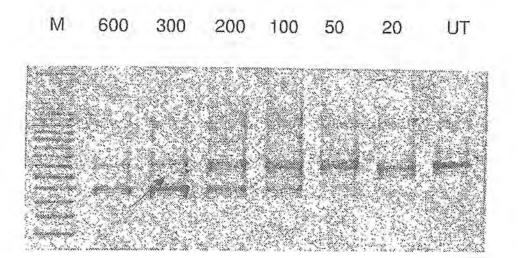


FIGURE 6

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H4A(+13+32)

M 600 300 100 50 20 UT Neg M

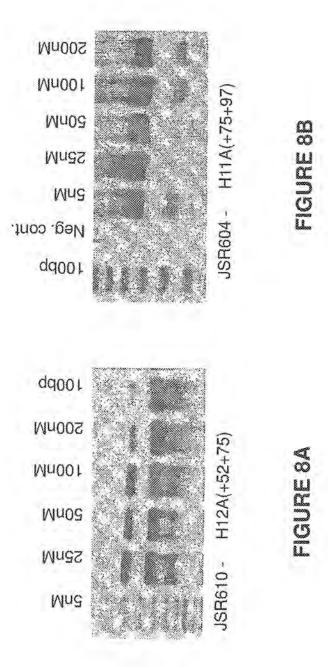
FIGURE 7

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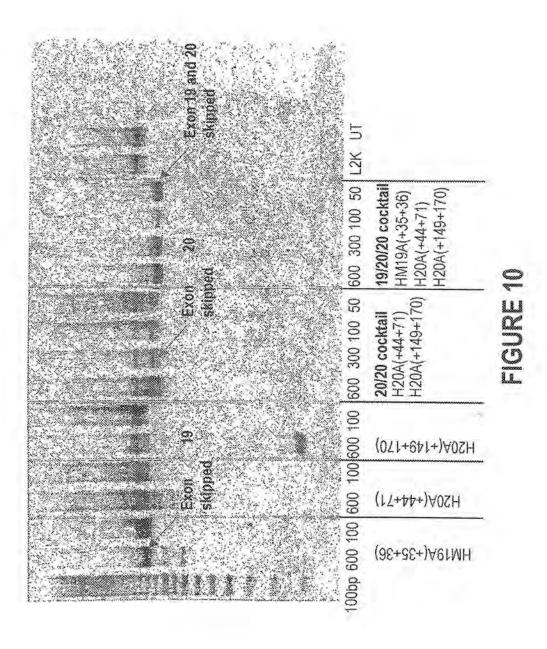


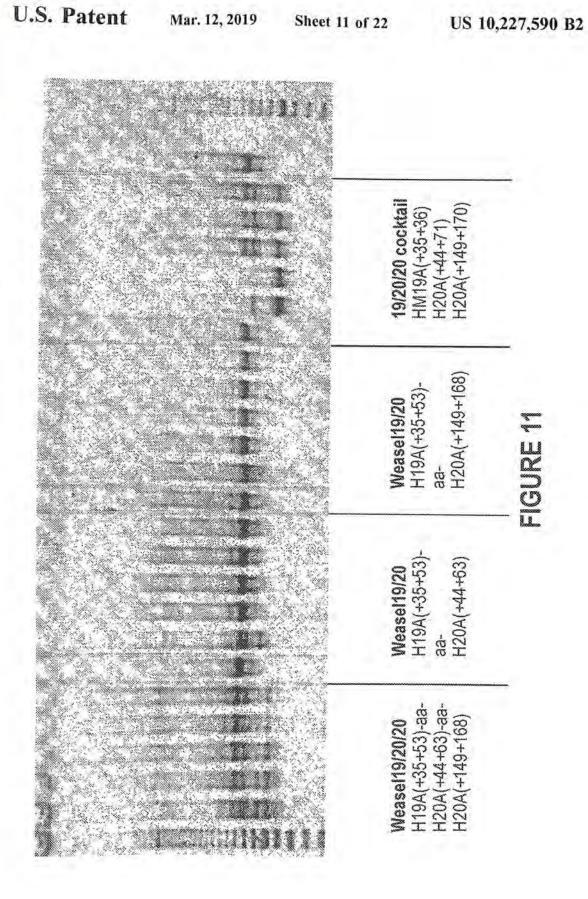
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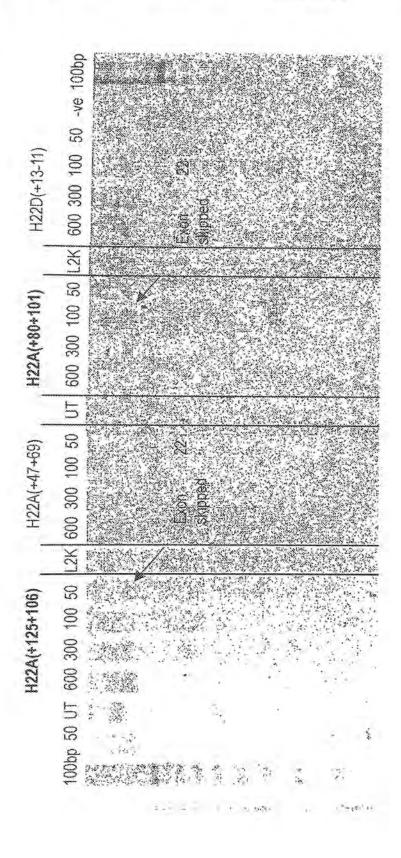
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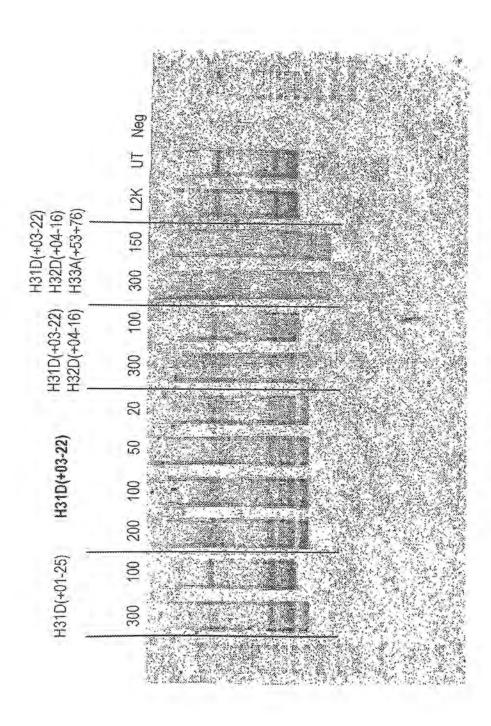




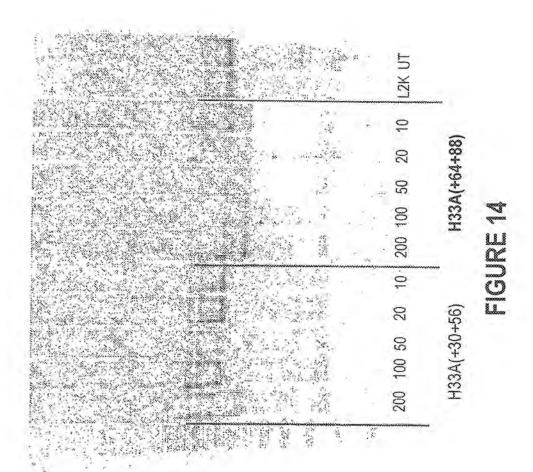
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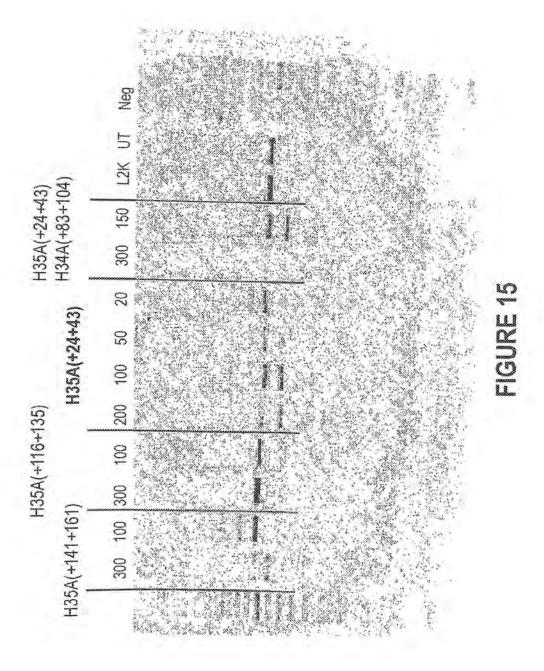
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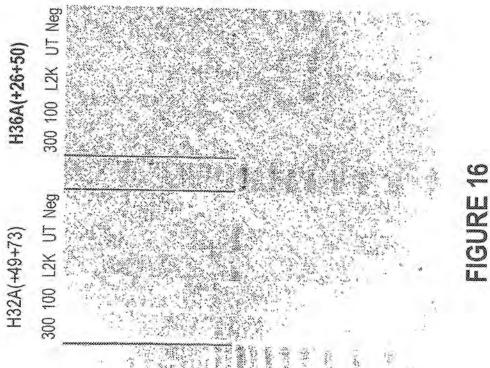
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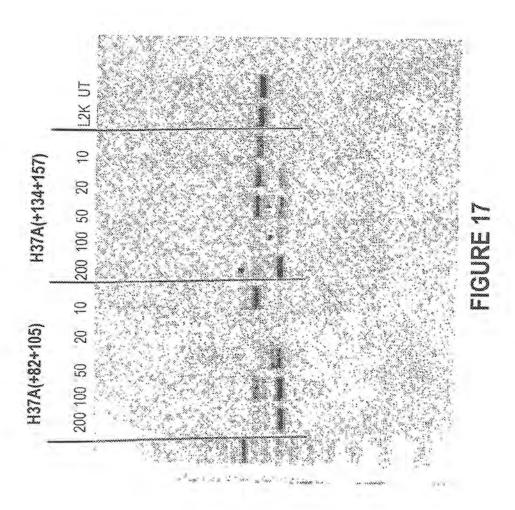
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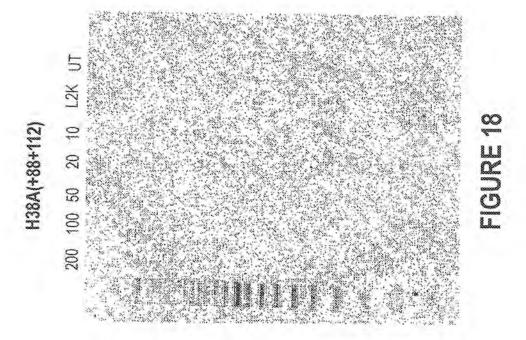
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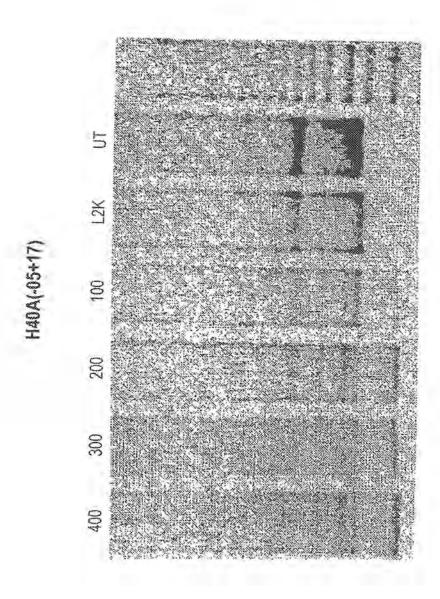
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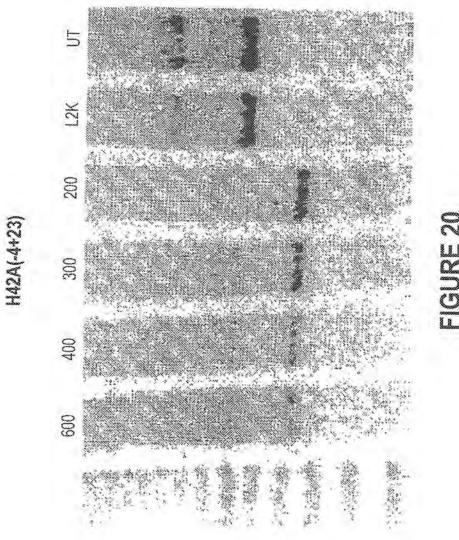


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H46A(+86+115)

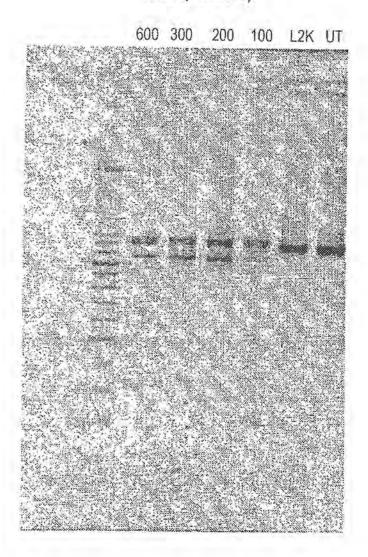
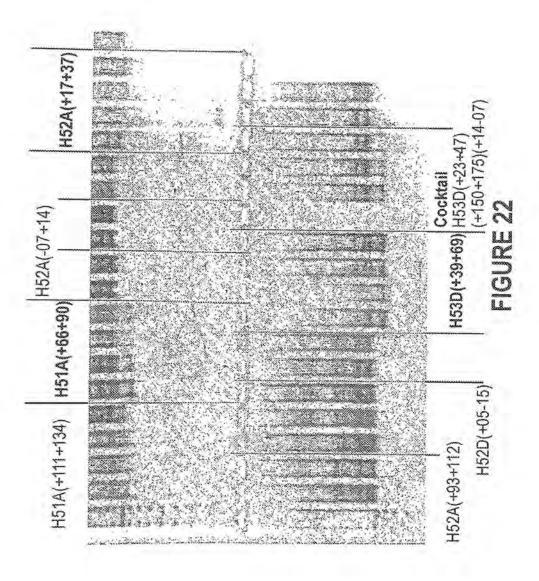


FIGURE 21

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## ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

# CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 15/274,772, filed Sep. 23, 2016, now pending, which application is a continuation of U.S. patent application Ser. No. 14/740,097, filed Jun. 15, 2015, now issued as U.S. Pat. No. 9,605,262, which application is a continuation of U.S. patent application Ser. No. 13/741,150, filed Jan. 14, 2013, now abandoned, which application is a continuation of U.S. patent application Ser. No. 13/168,857, filed Jun. 24, 2011, now abandoned, which application is a continuation of U.S. patent application Ser. No. 12/837,359, filed Jul. 15, 2010, now issued as U.S. Pat. No. 8,232,384, which application is a continuation of U.S. patent application Ser. No. 11/570,691, filed Jan. 15, 2008, now issued as U.S. Pat. No. 7,807,816, which application is a 35 U.S.C. § 371 National Phase Application of PCT/AU2005/000943, filed Jun. 28, 2005, which claims priority to Australian Patent Application No. 2004903474, filed Jun. 28, 2004; which applications are each incorporated herein by reference in their entireties.

# STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

This invention was made with government support under 30 grant number R01 NS044146 awarded by the National Institutes of Health. The government has certain rights in the invention.

#### STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with the application is provided in text format in liew of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is 4140.01500B0\_SL.txt. The text file is 62,078 bytes, was created on Aug. 23, 2018 and is being submitted electronically via EFS-Web.

## FIELD OF THE INVENTION

The present invention relates to novel antisense compounds and compositions suitable for facilitating exon skipping. It also provides methods for inducing exon skipping so using the novel antisense compounds as well as therapeutic compositions adapted for use in the methods of the invention.

### BACKGROUND ART

Significant effort is currently being expended researching methods for suppressing or compensating for disease-causing mutations in genes. Antisense technologies are being developed using a range of chemistries to affect gene expression at a variety of different levels (transcription, splicing, stability, translation). Much of that research has focused on the use of antisense compounds to correct or compensate for abnormal or disease-associated genes in a myriad of different conditions.

Antisense molecules are able to inhibit gene expression with exquisite specificity and because of this many research

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efforts concerning oligonucleotides as modulators of gene expression have focused on inhibiting the expression of targeted genes such as oncogenes or viral genes. The antisense oligonucleotides are directed either against RNA (sense strand) or against DNA where they form triplex structures inhibiting transcription by RNA polymerase II. To achieve a desired effect in specific gene down-regulation, the oligonucleotides must either promote the decay of the targeted mRNA or block translation of that mRNA, thereby effectively preventing de novo synthesis of the undesirable target protein.

Such techniques are not useful where the object is to up-regulate production of the native protein or compensate for mutations which induce premature termination of translation such as nonsense or frame-shifting mutations. Furthermore, in cases where a normally functional protein is prematurely terminated because of mutations therein, a means for restoring some functional protein production through antisense technology has been shown to be possible through intervention during the splicing processes (Sierakowska H, et al., (1996) Proc Natl Acad Sci USA 93, 12840-12844; Wilton S D, et al., (1999) Neuromusc Disorders 9, 330-338; van Deutekom J C et al., (2001) Human Mol Genet 10, 1547-1554). In these cases, the defective gene transcript should not be subjected to targeted degradation so the antisense oligonucleotide chemistry should not promote target mRNA decay.

In a variety of genetic diseases, the effects of mutations on the eventual expression of a gene can be modulated through a process of targeted exon skipping during the splicing process. The splicing process is directed by complex multiparticle machinery that brings adjacent exon-intron junctions in pre-mRNA into close proximity and performs cleavage of phosphodiester bonds at the ends of the introns with their subsequent reformation between exons that are to be spliced together. This complex and highly precise process is mediated by sequence motifs in the pre-mRNA that are relatively short semi-conserved RNA segments to which bind the various nuclear splicing factors that are then involved in the splicing reactions. By changing the way the splicing machinery reads or recognises the motifs involved in pre-mRNA processing, it is possible to create differentially spliced mRNA molecules. It has now been recognised that the majority of human genes are alternatively spliced during normal gene expression, although the mechanisms invoked have not been identified. Using antisense oligonucleotides, it has been shown that errors and deficiencies in a coded mRNA could be bypassed or removed from the mature gene transcripts.

In nature, the extent of genetic deletion or exon skipping in the splicing process is not fully understood, although many instances have been documented to occur, generally at very low levels (Sherrat T G, et al., (1993) Am J Hum Genet 53, 1007-1015). However, it is recognised that if exons associated with disease-causing mutations can be specifically deleted from some genes, a shortened protein product can sometimes be produced that has similar biological properties of the native protein or has sufficient biological activity to ameliorate the disease caused by mutations associated with the target exon (Lu Q L, et al., (2003) Nature Medicine 9, 1009-1014; Aartsma-Rus A et al., (2004) Am J Hum Genet 74: 83-92).

This process of targeted exon skipping is likely to be particularly useful in long genes where there are many exons and introns, where there is redundancy in the genetic constitution of the exons or where a protein is able to function without one or more particular exons (e.g. with the dystro-

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phin gene, which consists of 79 exons; or possibly some collagen genes which encode for repeated blocks of sequence or the huge nebulin or titin genes which are comprised of ~80 and over 370 exons, respectively).

Efforts to redirect gene processing for the treatment of 5 genetic diseases associated with truncations caused by mutations in various genes have focused on the use of antisense oligonucleotides that either: (1) fully or partially overlap with the elements involved in the splicing process; or (2) bind to the pre-mRNA at a position sufficiently close to the element to disrupt the binding and function of the splicing factors that would normally mediate a particular splicing reaction which occurs at that element (e.g., binds to the pre-mRNA at a position within 3, 6, or 9 nucleotides of the element to be blocked).

For example, modulation of mutant dystrophin premRNA splicing with antisense oligoribonucleotides has been reported both in vitro and in vivo. In one type of dystrophin mutation reported in Japan, a 52-base pair deletion mutation causes exon 19 to be removed with the 20 flanking introns during the splicing process (Matsuo et al., (1991) J Clin Invest., 87:2127-2131). An in vitro minigene splicing system has been used to show that a 31-mer 2'-O-methyl oligoribonucleotide complementary to the 5' half of the deleted sequence in dystrophin Kobe exon 19 25 mhibited splicing of wild-type pre-mRNA (Takeshima et al. (1995), J. Clin. Invest., 95, 515-520). The same oligonucleotide was used to induce exon skipping from the native dystrophin gene transcript in human cultured lymphoblastoid cells.

Dunckley et al., (1997) Nucleosides & Nucleotides, 16, 1665-1668 described in vitro constructs for analysis of splicing around exon 23 of mutated dystrophin in the mdx mouse mutant, a model for muscular dystrophy. Plans to analyse these constructs in vitro using 2' modified oligonucleotides targeted to splice sites within and adjacent to mouse dystrophin exon 23 were discussed, though no target sites or sequences were given.

2'-O-methyl oligoribonucleotides were subsequently reported to correct dystrophin deficiency in myoblasts from 40 the mdx mouse from this group. An antisense oligonucleotide targeted to the 3' splice site of murine dystrophin intron 22 was reported to cause skipping of the mutant exon as well as several flanking exons and created a novel in-frame dystrophin transcript with a novel internal deletion. This 45 mutated dystrophin was expressed in 1-2% of antisense treated mdx myotubes. Use of other oligonucleotide modifications such as 2'-O-methoxyethyl phosphodiesters are described (Dunckley et al. (1998) Human Mol. Genetics, 5, 1083-90)

Thus, antisense molecules may provide a tool in the treatment of genetic disorders such as Duchenne Muscular Dystrophy (DMD). However, attempts to induce exon skipping using antisense molecules have had mixed success. Studies on dystrophin exon 19, where successful skipping of 5s that exon from the dystrophin pre-mRNA was achieved using a variety of antisense molecules directed at the flanking splice sites or motifs within the exon involved in exon definition as described by Errington et al. (2003) *J Gen Med* 5, 518-527".

In contrast to the apparent ease of exon 19 skipping, the first report of exon 23 skipping in the mdx mouse by Dunckley et al., (1998) is now considered to be reporting only a naturally occurring revertant transcript or artefact rather than any true antisense activity. In addition to not 65 consistently generating transcripts missing exon 23, Dunckley et al., (1998) did not show any time course of induced

exon skipping, or even titration of antisense oligonucleotides, to demonstrate dose dependent effects where the levels of exon skipping corresponded with increasing or decreasing amounts of antisense oligonucleotide. Furthermore, this work could not be replicated by other researchers.

The first example of specific and reproducible exon skipping in the mdx mouse model was reported by Wilton et al., (1999) Neuromuscular Disorders 9, 330-338. By directing an antisense molecule to the donor splice site, consistent and efficient exon 23 skipping was induced in the dystrophin mRNA within 6 hours of treatment of the cultured cells. Wilton et al., (1999), also describe targeting the acceptor region of the mouse dystrophin pre-mRNA with longer antisense oligonucleotides and being unable to repeat the published results of Dunckley et al., (1998). No exon skipping, either 23 alone or multiple removal of several flanking exons, could be reproducibly detected using a selection of antisense oligonucleotides directed at the acceptor splice site of intron 22.

While the first antisense oligonucleotide directed at the intron 23 donor splice site induced consistent exon skipping in primary cultured myoblasts, this compound was found to be much less efficient in immortalized cell cultures expressing higher levels of dystrophin. However, with refined targeting and antisense oligonucleotide design, the efficiency of specific exon removal was increased by almost an order of magnitude (see Mann C J et al., (2002) J Gen Med 4, 644-654).

Thus, there remains a need to provide antisense oligonucleotides capable of binding to and modifying the splicing of a target nucleotide sequence. Simply directing the antisense oligonucleotides to motifs presumed to be crucial for splicing is no guarantee of the efficacy of that compound in a therapeutic setting.

### SUMMARY OF THE INVENTION

The present invention provides antisense molecule compounds and compositions suitable for binding to RNA motifs involved in the splicing of pre-mRNA that are able to induce specific and efficient exon skipping and a method for their use thereof.

The choice of target selection plays a crucial role in the efficiency of exon skipping and hence its subsequent application of a potential therapy. Simply designing antisense molecules to target regions of pre-mRNA presumed to be involved in splicing is no guarantee of inducing efficient and specific exon skipping. The most obvious or readily defined targets for splicing intervention are the donor and acceptor splice sites although there are less defined or conserved motifs including exonic splicing enhancers, silencing elements and branch points.

The acceptor and donor splice sites have consensus sequences of about 16 and 8 bases respectively (see FIG. 1 for schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process).

According to a first aspect, the invention provides antisense molecules capable of binding to a selected target to 60 induce exon skipping.

For example, to induce exon skipping in exons 3 to 8, 10 to 16, 19 to 40, 42 to 44, 46, 47, and 50 to 53 in the Dystrophin gene transcript the antisense molecules are preferably selected from the group listed in Table 1A.

In a further example, it is possible to combine two or more antisense oligonucleotides of the present invention together to induce multiple exon skipping in exons 19-20, and 53.

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This is a similar concept to targeting of a single exon. A combination or "cocktail" of antisense oligonucleotides are directed at adjacent exons to induce efficient exon skipping.

In another example, to induce exor skipping in exons 19-20, 31, 34 and 53 it is possible to improve exon skipping of a single exon by joining together two or more antisense oligonucleotide molecules. This concept is termed by the inventor as a "weasel", an example of a cunningly designed antisense oligonucleotide. A similar concept has been described in Aartsma-Rus A et al., (2004) Am J Hum Genet 10, 74: 83-92).

According to a second aspect, the present invention provides antisense molecules selected and or adapted to aid in the prophylactic or therapeutic treatment of a genetic disorder comprising at least an antisense molecule in a form 15 suitable for delivery to a patient.

According to a third aspect, the invention provides a method for treating a patient suffering from a genetic disease wherein there is a mutation in a gene encoding a particular protein and the affect of the mutation can be abrogated by 20 exon skipping, comprising the steps of: (a) selecting an antisense molecule in accordance with the methods described herein; and (b) administering the molecule to a patient in need of such treatment.

The invention also addresses the use of purified and 25 isolated antisense oligonucleotides of the invention, for the manufacture of a medicament for treatment of a genetic disease.

The invention further provides a method of treating a condition characterised by Duchenne muscular dystrophy.

30 which method comprises administering to a patient in need of treatment an effective amount of an appropriately designed antisense oligonucleotide of the invention, relevant to the particular genetic lesion in that patient. Further, the invention provides a method for prophylactically treating a patient to prevent or at least minimise Duchene muscular dystrophy, comprising the step of: administering to the patient an effective amount of an antisense oligonucleotide or a pharmaceutical composition comprising one or more of these biological molecules.

The invention also provides kits for treating a genetic disease, which kits comprise at least a antisense oligonucleotide of the present invention, packaged in a suitable container and instructions for its use.

Other aspects and advantages of the invention will 45 become apparent to those skilled in the art from a review of the ensuing description, which proceeds with reference to the following figures.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 Schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process (SEQ ID NOS: 213 and 214).

FIG. 2. Diagrammatic representation of the concept of 55 antisense oligonucleotide induced exon skipping to by-pass disease-causing mutations (not drawn to scale). The hatched box represents an exon carrying a mutation that prevents the translation of the rest of the mRNA into a protein. The solid black bar represents an antisense oligonucleotide that prevents inclusion of that exon in the mature mRNA.

FIG. 3 Gel electrophoresis showing differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. The preferred compound [H8A(-06+18)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured normal human muscle cells. The less preferred antisense oligonucleotide

[H8A(-06+14)] also induces efficient exon skipping, but at much higher concentrations. Other antisense oligonucleotides directed at exon 8 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

FIG. 4 Gel electrophoresis showing differing efficiencies of two antisense molecules directed at internal domains within exon 7, presumably exon splicing enhancers. The preferred compound [H7A(+45+67)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells. The less preferred antisense oligonucleotide [H7A(+2+26)] induces only low levels of exon skipping at the higher transfection concentrations. Other antisense oligonucleotides directed at exon 7 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

FIG. 5 Gel electrophoresis showing an example of low efficiency exon 6 skipping using two non-preferred antisense molecules directed at human exon 6 donor splice site. Levels of induced exon 6 skipping are either very low [H6D(+04–21)] or almost undetectable [H6D(+18–04)]. These are examples of non-preferred antisense oligonucleotides to demonstrate that antisense oligonucleotide design plays a crucial role in the efficacy of these compounds.

FIG. 6 Gel electrophoresis showing strong and efficient human exon 6 skipping using an antisense molecules [H6A(+69+91)] directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells.

FIG. 7 Gel electrophoresis showing strong human exon 4 skipping using an antisense molecule H4A(+13+32) directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells,

FIG. 8A Gel electrophoresis showing strong human exon 12 skipping using antisense molecule H12A(+52+75) directed at exon 12 internal domain.

FIG. 8B Gel electrophoresis showing strong human exon 11 skipping using antisense molecule H11A(+75+97) directed at an exon 11 internal domain.

FIG. 9A Gel electrophoresis showing strong human exon 15 skipping using antisense molecules H15A(+48+71) and H15A(-12+19) directed at an exon 15 internal domain.

FIG. 9B Gel electrophoresis showing strong human exon 16 skipping using antisense molecules H16A(-12+19) and H16A(-06+25).

FIG. 10 Gel electrophoresis showing human exon 19/20 skipping using antisense molecules H20A(+44+71) and H20A(+149+170) directed at an exon 20 and a "cocktail" of antisense oligonucleotides H19A(+35+65, H20A(+44+71) and H20A(+149+170) directed at exons 19/20.

FIG. 11 Gel electrophoresis showing human exon 19/20 skipping using "weasels" directed at exons 19 and 20.

FIG. 12 Gel electrophoresis showing exon 22 skipping using antisense molecules H22A(+125+106), H22A(+47+69), H22A(+80+101) and H22D(+13-11) directed at exon 22.

FIG. 13 Gel electrophoresis showing exon 31 skipping using antisense molecules H31D(+01-25) and H31D(+03-22); and a "cocktail" of antisense molecules directed at exon 31

FIG. 14 Gel electrophoresis showing exon 33 skipping using antisense molecules H33A(+30+56) and H33A(+64+88) directed at exon 33.

FIG. 15 Gel electrophoresis showing exon 35 skipping using antisense molecules H35A(+141+161), H35A(+116+

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135), and H35A(+24+43) and a "cocktail of two antisense molecules, directed at exon 35.

FIG. 16 Gel electrophoresis showing exon 36 skipping using antisense molecules H32A(+49+73) and H36A(+26+50) directed at exon 36.

FIG. 17 Gel electrophoresis showing exon 37 skipping using antisense molecules H37A(+82+105) and H37A(+134+157) directed at exon 37.

FIG. 18 Gel electrophoresis showing exon 38 skipping using antisense molecule H38A(+88+112) directed at exon 10 38.

FIG. 19 Gel electrophoresis showing exon 40 skipping using antisense molecule H40A(-05+17) directed at exon 40.

FIG. 20 Gel electrophoresis showing exon 42 skipping

using antisense molecule H42A(-04+23) directed at exon 42.

FIG. 21 Gel electrophoresis showing exon 46 skipping 5 using antisense molecule H46A(+86+115) directed a# exon 46

FIG. 22 Gel electrophoresis showing exon 51, exon 52 and exon 53 skipping using various antisense molecules directed at exons 51, 52 and 53, respectively. A "cocktail" of antisense molecules is also shown directed at exon 53.

# BRIEF DESCRIPTION OF THE SEQUENCE LISTINGS

#### TABLE 1A

Description of 2'-0-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-0-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ | SEQUENCE     | NUCLEOTIDE SEQUENCE (5' - 3')                |
|-----|--------------|--|
| 1   | H8A(-06+18)  | GAU AGG UGG UAU CAA CAU CUG UAA              |
| 2   | H8A (-03+18) | GAU AGG UGG UAU CAA CAU CUG                  |
| 3   | H8A(-07+18)  | GAU AGG UGG UAU CAA CAU CUG UAA G            |
| 4   | H8A(-06+14)  | GGU GGU AUC AAC AUC UGU AA                   |
| 5   | H8A (-10+10) | GUA UCA ACA UCU GUA AGC AC                   |
| 6   | H7A (+45+67) | UGC AUG UUC CAG UCG UUG UGU GG               |
| 7   | H7A(+02+26)  | CAC UAU UCC AGU CAA AUA GGU CUG G            |
| 8   | H7D(+15-10)  | AUU UAC CAA CCU UCA GGA UCG AGU A            |
| 9   | H7A(-18+03)  | GGC CUA AAA CAC AUA CAC AUA                  |
| 10  | C6A(-10+10)  | CAU DUU UGA CCU ACA DGU GG                   |
| 11  | C6A(+14+06)  | UUU GAC CUA CAU GUG GAA AG                   |
| 12  | C6A(-14+12)  | UAC AUU UUU GAC CUA CAU GUG GAA AG           |
| 13  | C6A(-13+09)  | AUU DUU GAC CUA CAU GGG AAA G                |
| 14  | CH6A(+69+91) | UAC GAG UUG AUU GUC GGA CCC AG               |
| 15  | C6D(+12-13)  | GUG GUC UCC UUA CCU AUG ACU GUG G            |
| 16  | C6D(+06-11)  | GGU CUC CUU ACC UAU GA                       |
| 17  | H6D(+04-21)  | UGU CUC AGU AAU CUU CUU ACC UAU              |
| 18  | H6D(+18-04)  | UCU DAC CUA UGA CUA UGG AUG AGA              |
| 19  | H4A(+13+32)  | GCA UGA ACU CUU GUG GAU CC                   |
| 20  | H4D(+04-16)  | CCA GGG UAC UAC UUA CAU UA                   |
| 21  | H4D (-24-44) | AUC GUG UGU CAC AGC AUC CAG                  |
| 22  | H4A(+11+40)  | UGU UCA GGG CAU GAA CUC UUG UGG AUC          |
| 23  | H3A(+30+60)  | UAG GAG GCG CCU CCC AUC CUG UAG GUC<br>ACU G |
| 24  | H3A (+35+65) | AGG UCU AGG AGG CGC CUC CCA UCC UGU<br>AGG U |
| 25  | H3A(+30+54)  | GCG CCU CCC AUC CUG UAG GUC ACU G            |

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## TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ |                | Or morpholinos, these U bases may be shown as "T".  NUCLEOTIDE SEQUENCE (5' - 3') |
|-----|----------------|---|
| 26  | H3D(+46-21)    | CUU CGA GGA GGU CUA GGA GGC GCC UC  |
| 27  | H3A(+30+50)    | CUC CCA UCC UGU AGG UCA CUG   |
| 28  | H3D(+19-03)    | UAC CAG UUU UUG CCC UGU CAG G   |
| 29  | H3A(-06+20)    | UCA AUA UGC UGC UUC CCA AAC UGA AA  |
| 30  | H3A(+37+61)    | CUA GGA GGC GCC UCC CAU CCU GUA G   |
| 31  | H5A(+20+50)    | UDA DGA UUU CCA UCU ACG ADG UCA GDA   |
| 32  | H5D(+25-05)    | CUU ACC UGC CAG UGG AGG AUU AUA UUC   |
| 33  | H5D(+10-15)    | CAU CAG GAU DOU DAC CUG CCA GUG G   |
| 34  | H5A(+10+34)    | CGA UGU CAG UAC UUC CAA UAU UCA C   |
| 35  | H5D(-04-21)    | ACC AUU CAU CAG GAU UCU   |
| 36  | H5D(+16-02)    | ACC UGC CAG UGG AGG AUU   |
| 37  | H5A(-07+20)    | CCÁ AUA UUC ACU AAA UCA ACC UGU UAA   |
| 38  | H5D(+18-12)    | CAG GAU UGU UAC CUG CCA GUG GAG GAU<br>UAU  |
| 39  | H5A(+05+35)    | ACG AUG UCA GUA CUU CCA AUA UUC ACU   |
| 40  | H5A(+15+45)    | AUD UCC AUC UAC GAU GUC AGU ACU UCC AAU A   |
| 41  | H10A(-05+16)   | CAG GAG CUU CCA AAU GCU GCA   |
| 42  | H10A(-05+24)   | CUU GUC UUC AGG AGC UUC CAA AUG CUG CA  |
| 43  | H10A(+98+119)  | UCC UCA GCA GAA AGA AGC CAC G   |
| 44  | H10A(+130+149) | UUA GAA AUC UCU CCU UGU GC  |
| 45  | H10A(-33-14)   | UAA AUU GGG UGU UAC ACA AU  |
| 46  | H11D(+26+49)   | CCC UGA GGC AUU CCC AUC UUG AAU   |
| 47  | H11D(+11-09)   | AGG ACU UAC UUG CUU UGU UU  |
| 48  | H11A(+118+140) | CUU GAA UUU AGG AGA UUC AUC UG  |
| 49  | H11A(+75+97)   | CAU CUU CUG AUA AUU UUC CUG UU  |
| 50  | H12A(+52+75)   | UCU UCU GUU UUU GUU AGC CAG UCA   |
| 51  | H12A(-10+10)   | UCU AUG UAA ACU GAA AAU UU  |
| 52  | H12A(+11+30)   | UUC UGG AGA UCC AUU AAA AC  |
| 53  | H13A(+77+100)  | CAG CAG UUG CGU GAU CUC CAC UAG   |
| 54  | H13A(+55+75)   | UUC AUC AAC UAC CAC CAC CAU   |
| 55  | H13D(+06-19)   | CUA AGC AAA AUA AUC UGA CCU UAA G   |
|     | H14A(+37+64)   | CUU GUA AAA GAA CCC AGC GGU CUU CUG U   |
|     | H14A(+14+35)   | CAU CUA CAG AUG UUU GCC CAU C   |
|     | H14A(+51+73)   | GAA GGA UGU CUU GUA AAA GAA CC  |

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## TABLE 1A-continued

Description of 2'-O-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ | SEQUENCE       | NUCLEOTIDE SEQUENCE (5' - 3')                |
|-----|----------------|--|
| 59  | H14D(-02+18)   | ACC UGU UCU UCA GUA AGA CG                   |
| 60  | H14D(+14-10)   | CAU GAC ACA CCU GUU CUU CAG UAA              |
| 61  | H14A(+61+80)   | CAU UUG AGA AGG AUG UCU UG                   |
| 62  | H14A(-12+12)   | AUC UCC CAA UAC CUG GAG AAG AGA              |
| 63  | H15A(-12+19)   | GCC AUG CAC UAA AAA GGC ACU GCA AGA          |
| 64  | H15A(+48+71)   | UCU UUA AAG CCA GUU GUG UGA AUC              |
| 65  | H15A(+08+28)   | UUU CUG AAA GCC AUG CAC UAA                  |
| 66  | H15D(+17-08)   | GUA CAU ACG GCC AGU UUU UGA AGA C            |
| 67  | H16A(-12+19)   | CUA GAU CCG CUU UUA AAA CCU GUU AAA<br>ACA A |
| 68  | H16A(-06+25)   | UCU UUU CUA GAU CCG CUU UUA AAA CCU          |
| 69  | H16A(-06+19)   | CUA GAU CCG CUU UUA AAA CCU GUU A            |
| 70  | H16A(+87+109)  | CCG UCU UCU GGG UCA CUG ACU UA               |
| 71  | H16A(-07+19)   | CUA GAU CCG CUU UUA AAA CCU GUU AA           |
| 72  | H16A(-07+13)   | CCG CUU UUA AAA CCU GUU AA                   |
| 73  | H16A(+12+37)   | UGG AUU GCU UUU UCU UUU CUA GAU CC           |
| 74  | H16A(+92+116)  | CAU GCU UCC GUC UUC UGG GUC ACU G            |
| 75  | H16A(+45+67)   | G AUC UUG UUU GAG UGA AUA CAG U              |
| 76  | H16A(+105+126) | GUU AUC CAG CCA UGC UUC CGU C                |
| 77  | H16D(+05-20)   | UGA UAA UUG GUA UCA CUA ACC UGU G            |
| 78  | H16D(+12-11)   | GUA UCA CUA ACC UGU GCU GUA C                |
| 79  | H19A(+35+53)   | CUG CUG GCA UCU UGC AGU U                    |
| 80  | H19A(+35+65)   | GCC UGA GCU GAU CUG CUG GCA UCU UGC<br>AGU U |
| 81  | H20A(+44+71)   | CUG GCA GAA UUC GAU CCA CCG GCU GUU C        |
| 92  | H20A(+147+168) | CAG CAG UAG UUG UCA UCU GCU C                |
| 83  | H20A(+185+203) | UGA UGG GGU GGU GGG UUG G                    |
| 84  | H20A(-08+17)   | AUC UGC AUU AAC ACC CUC UAG AAA G            |
| 85  | H2OA(+30+53)   | CCG GCU GUU CAG UUG UUC UGA GGC              |
| 86  | H20A(-11+17)   | AUC UGC AUU AAC ACC CUC UAG AAA GAA A        |
| 87  | H20D(+08-20)   | GAA GGA GAG AUU CUU ACC UUA CAA A            |
| 88  | H20A(+44+63)   | AUU CGA UCC ACC GGC UGU UC                   |
| 89  | H20A(+149+168  | CAG CAG UAG UUG UCA UCU GC                   |
|     | H21A(-Q6+16)   | GCC GGU UGA CUU CAU CCU GUG C                |
|     | H21A(+85+106)  | CUG CAU CCA GGA ACA UGG GUC C                |
|     | H21A(+85+108)  | GUC UGC AUC CAG GAA CAU GGG UC               |
|     |                |  |

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## TABLE 1A-continued

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Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ | SEQUENCE       | NUCLEOTIDE SEQUENCE (5' - 3')       |
|-----|----------------|-------------------------------------|
| 93  | H21A(+08+31)   | GUU GAA GAU CUG AUA GCC GGU UGA     |
| 94  | H21D(+18-07)   | UAC UUA CUG UCU GUA GCU CUU UCU     |
| 95  | H22A(+22+45)   | CAC UCA UGG UCU CCU GAU AGC GCA     |
| 96  | H22A(+125+106) | CUG CAA UUC CCC GAG UCU CUG C       |
| 97  | H22A(+47+69)   | ACU GCU GGA CCC AUG UCC UGA UG      |
| 98  | H22A(+80+101)  | CUA AGU UGA GGU AUG GAG AGU         |
| 99  | H22D(+13-11)   | UAU UCA CAG ACC UGC AAU UCC CC      |
| 100 | H23A(+34+59)   | ACA GUG GUG CUG AGA UAG UAU AGG CC  |
| 101 | H23A(+18+39)   | UAG GCC ACU UUG UUG CUC UUG C       |
| 102 | H23A(+72+90)   | UUC AGA GGG CGC UUU CUU C           |
| 103 | H24A(+48+70)   | GGG CAG GCC AUU CCU CCU UCA GA      |
| 104 | H24A(-02+22)   | UCU UCA GGG UUU GUA UGU GAU UCU     |
| 105 | H25A(+9+36)    | CUG GGC UGA AUU GUC UGA AUA UCA CUG |
| 106 | H25A(+131+156) | CUG UUG GCA CAU GUG AUC CCA CUG AG  |
| 107 | H25D(+16-08)   | GUC UAU ACC UGU UGG CAC AUG UGA     |
| 108 | H26A(+132+156) | UGC UUU CUG UAA UUC AUC UGG AGU U   |
| 109 | H26A(-07+19)   | CCU CCU UUC UGG CAU AGA CCU UCC AC  |
| 110 | H26A(+68+92)   | UGU GUC AUC CAU UCG UGC AUC UCU G   |
| 111 | H27A(+82+106)  | UUA AGG CCU CUU GUG CUA CAG GUG G   |
| 112 | H27A(-4+19)    | GGG GCU CUU CUU UAG CUC UCU GA      |
| 113 | H27D(+19-03)   | GAC UUC CAA AGU CUU GCA UUU C       |
| 114 | H28A(-05+19)   | GCC AAC AUG CCC AAA CUU CCU AAG     |
| 115 | H28A(+99+124)  | CAG AGA UUU CCU CAG CUC CGC CAG GA  |
| 116 | H28D(+16-05)   | CUU ACA UCU AGC ACC UCA GAG         |
| 117 | H29A(+57+81)   | UCC GCC AUC UGU UAG GGU CUG UGC C   |
| 118 | H29A(+18+42)   | AUU UGG GUU AUC CUC UGA AUG UCG C   |
| 119 | H29D(+17-05)   | CAU ACC UCU UCA UGU AGU UCC C       |
| 20  | H30A(+122+147) | CAU UUG AGC UGC GUC CAC CUU GUC UG  |
| 21  | H30A(+25+50)   | UCC UGG GCA GAC UGG AUG CUC UGU UC  |
|     | H30D(+19-04)   | UUG CCU GGG CUU CCU GAG GCA UU      |
|     | H31D(+06-18)   | UUC UGA AAU AAC AUA UAC CUG UGC     |
|     | H31D(+03-22)   | UAG UUU CUG AAA UAA CAU AUA CCU G   |
|     | H31A(+05+25)   | GAC UUG UCA AAU CAG AUU GGA         |
|     | H31D(+04-20)   | GUU UCU GAA AUA ACA UAU ACC UGU     |
|     | H32D(+04-16)   | CAC CAG AAA UAC AUA CCA CA          |

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# TABLE 1A-continued

Description of 2'-O-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ   | SEQUENCE       | or morpholinos, these U bases may be shown as "T".  NUCLEOTIDE SEQUENCE (5' - 3') |
|-------|----------------|---|
| 128   | H32A(+151+170) | CAA UGA UUU AGC UGU GAC UG  |
| 129   | H32A(+10+32)   | CGA AAC UUC AUG GAG ACA UCU UG  |
| 130   | H32A(+49+73)   | CUU GUA GAC GCU GCU CAA AAU UGG C   |
| 131   | H33D(+09-11)   | CAU GCA CAC ACC UUU GCU CC  |
| 132   | H33A(+53+76)   | UCU GUA CAA UCU GAC GUC CAG UCU   |
| 133   | H33A(+30+56)   | GUC DUU AUC ACC AUD UCC ACU UCA GAC   |
| 134   | H33A(+64+88)   | CCG UCU GCU UUU UCU GUA CAA UCU G   |
| 135   | H34A(+83+104)  | UCC AUA UCU GUA GCU GCC AGC C   |
| 136   | H34A(+143+165) | CCA GGC AAC UUC AGA AUC CAA AU  |
| 13.7  | H34A(-20+10)   | UUU CUG UUA CCU GAA AAG AAU UAU AAU<br>GAA  |
| 138   | H34A(+46+70)   | CAU UCA UUU CCU UUC GCA UCU UAC G   |
| 139   | H34A(+95+120)  | UGA UCU CUU UGU CAA UUC CAU AUC UG  |
| 140   | H34D(+10-20)   | UUC AGU GAU AUA GGU UUU ACC UUU CCC   |
| 141   | H34A(+72+96)   | CUG UAG CUG CCA GCC AUU CUG UCA AG  |
| 142   | H35A(+141+161) | UCU UCU GCU CGG GAG GUG ACA   |
| 143   | H35A(+116+135) | CCA GUU ACU AUU CAG AAG AC  |
| 144   | H35A(+24+43)   | UCU UCA GGU GCA CCU UCU GU  |
| 145   | H36A(+26+50)   | UGU GAU GUG GUC CAC AUU CUG GUC A   |
| 146   | H36A(-02+18)   | CCA UGU GUU UCU GGU AUU CC  |
| 147   | H37A(+26+50)   | CGU GUA GAG UCC ACC UUU GGG CGU A   |
| 148   | H37A(+82+105)  | UAC UAA UUU CCU GCA GUG GUC ACC   |
| 149   | H37A(+134+157) | DUC UGU GUG AAA UGG CUG CAA AUC   |
| 150   | H38A(-01+19)   | CCU UCA AAG GAA UGG AGG CC  |
| 151   | H38A(+59+83)   | UGC UGA AUU UCA GCC UCC AGU GGU U   |
| 152   | H38A(+88+112)  | UGA AGU CUU CCU CUU UCA GAU UCA C   |
|       | H39A(+62+85)   | CUG GCU UUC UCU CAU CUG UGA UUC   |
|       | H39A(+39+58)   | GUU GUA AGU UGU CUC CUC UU  |
|       | H39A(+102+121) | UUG UCU GUA ACA GCU GCU GU  |
|       | H39D(+10-10)   | GCU CUA AUA CCU UGA GAG CA  |
|       | H40A(-05+17)   | CUU UGA GAC CUC AAA UCC UGU U   |
|       |                | CUU UAU UUU CCU UUC AUC UCU GGG C   |
|       | H40A(+129+153) | AUC GUU UCU UCA CGG ACA GUG UGC UGG   |
|       | H42A(-04+23)   | GGG CUU GUG AGA CAU GAG UGA UUU   |
|       | H42A(+86+109)  | A CCU UCA GAG GAC UCC UCU UGC   |
| 161 1 | H42D(+19-02)   | UAU GUG UUA CCU ACC CUU GUC GGU C   |
| 162 I | H43D(+10-15)   | and and and are me con and and a  |

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# TABLE 1A-continued

Description of 2'-0-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-0-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ | SEQUENCE                   | or morpholinos, these U bases may be shown as "T".  NUCLEOTIDE SEQUENCE (5' ~ 3') |
|-----|----------------------------|---|
| 163 | H43A(+101+120)             | GGA GAG AGC UUC CUG UAG CU  |
| 164 | H43A(+78+100)              | UCA CCC UUU CCA CAG GCG UUG CA  |
| 165 | H44A(+85+104)              | UUU GUG UCU UUC UGA GAA AC  |
| 166 | H44D(+10-10)               | AAA GAC UUA CCU UAA GAU AC  |
| 167 | H44A(-06+14)               | AUC UGU CAA AUC GCC UGC AG  |
| 168 | H46D(+16-04)               | UUA CCU UGA CUU GCU CAA GC  |
| 169 | H46A(+90+109)              | UCC AGG UUC AAG UGG GAU AC  |
| 170 | H47A(+76+100)              | GCU CUU CUG GGC DUA UGG GAG CAC U   |
| 171 | H47D(+25-02)               | ACC UUU AUC CAC UGG AGA UUU GUC UGC   |
| 172 | H47A(-9+12)                | UUC CAC CAG UAA CUG AAA CAG   |
| 173 | H50A(+02+30)               | CCA CUC AGA GCU CAG AUC UUC UAA CUU CC  |
| 174 | H50A(+07+33)               | CUU CCA CUC AGA GCU CAG AUC UUC UAA   |
| 175 | H50D(+07-18)               | GGG AUC CAG UAU ACU UAC AGG CUC C   |
| 176 | H51A(-01+25)               | ACC AGA GUA ACA GUC UGA GUA GGA GC  |
| 177 | H51D(+16-07)               | CUC AUA CCU UCU GCU UGA UGA UC  |
| 178 | H51A(+111 +134)            | DUC UGU CCA AGC CCG GUU GAA AUC   |
| 179 | H51A(+61+90)               | ACA UCA AGG AAG AUG GCA UUU CUA GUU<br>UGG  |
| 180 | H51A(+66+90)               | ACA UCA AGG AAG AUG GCA UUU CUA G   |
| 181 | H51A(+66+95)               | CUC CAA CAU CAA GGA AGA UGG CAU UUC<br>UAG  |
| 182 | H51D(+08-17)               | AUC AUU UUU UCU CAU ACC UUC UGC U   |
| 193 | H51A/D(+08-17)<br>& (-15+) | AUC AUU UUU DCU CAU ACC UUC UGC UAG<br>GAG CUA AAA                                |
| 184 | H51A(+175+195)             | CAC CCA CCA UCA CCC UCU GUG   |
| 185 | H51A(+199+220)             | AUC AUC UCG UUG AUA UCC UCA A   |
| 186 | H52A(-07+14)               | UCC UGC AUU GUU GCC UGU AAG   |
| 187 | H52A(+12+41)               | UCC AAC UGG GGA CGC CUC UGU UCC AAA<br>UCC  |
| 188 | H52A(+17+37)               | ACU GGG GAC GCC UCU GUU CCA   |
| 189 | H52A(+93+112)              | CCG UAA UGA UUG UUC UAG CC  |
| 190 | H52D(+05-15)               | UGU UAA AAA ACU UAC DUC GA  |
| 191 | H53A(+45+69)               | CAU UCA ACU GUU GCC UCC GGU UCU G   |
| 192 | H53A(+39+62)               | CUG UUG CCU CCG GUU CUG AAG GUG   |
| 193 | H53A(+39+69)               | CAU UCA ACU GUU GCC UCC GGU UCU GAA<br>GGU G                                      |
| 194 | H53D(+14-07)               | UAC UAA CCU UGG UUU CUG UGA   |
|     | R53A(+23+47)               | CUG AAG GUG UUC UUG UAC UUC AUC C   |

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## TABLE 1A-continued

Description of 2'-O-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such

| SEQ |                | or morpholinos, these U bases may be shown as "T".  NUCLEOTIDE SEQUENCE (5' - 3') |
|-----|----------------|---|
| 196 | H53A(+150+176) | UGU AUA GGG ACC CUC CUU CCA UGA CUC   |
| 197 | H53D(+20-05)   | CUA ACC UUG GUU UCU GUG AUU UUC U   |
| 198 | H53D(+09-18)   | GGU AUC UUU GAU ACU AAC CUU GGU UUC   |
| 199 | H53A(-12+10)   | AUU CUU UCA ACU AGA AUA AAA G   |
| 200 | H53A(-07+18)   | GAU UCU GAA UUC UUU CAA CUA GAA U   |
| 201 | H53A(+07+26)   | AUC CCA CUG AUU CUG AAU UC  |
| 202 | H53A(+124+145) | UUG GCU CUG GCC UGU CCU AAG A   |
| 203 | H46A(+86+115)  | CUC UUU UCC AGG UUC AAG UGG GAU ACU   |
| 204 | H46A(+107+137) | CAA GCU UUU CUU UUA GUU GCU GCU CUU   |
| 205 | H46A(-10+20)   | UAU UCU UUU GUU CUU CUA GCC UGG AGA<br>AAG  |
| 206 | H46A(+50+77)   | CUG CUU CCU CCA ACC AUA AAA CAA AUU C   |
| 207 | H45A(-06+20)   | CCA AUG CCA UCC UGG AGU UCC UGU AA  |
| 208 | H45A(+91 +110) | UCC UGU AGA AUA CUG GCA UC  |
| 209 | H45A(+125+151) | UGC AGA CCU CCU GCC ACC GCA GAU UCA   |
| 210 | H45D(+16 -04)  | CUA CCU CUU UUU UCU GUC UG  |
| 211 | H45A(+71+90)   | UGU UUU UGA GGA UUG CUG AA  |

### TABLE 1B

Description of a cocktail of 2'-0-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

|   | Q<br>D | SEQUENCE       | NUC | LEOT | IDE : | SEQU | ENCE | (5' | -3') |     |
|---|--------|----------------|-----|------|-------|------|------|-----|------|-----|
| 8 | 1      | H20A(+44+71)   | CUG | GCA  | GAA   | nnc  | GAU  | CCA | CCG  | GCU |
| 8 | 2      | H20A(+147+168) | GUU | C    |       |      |      |     |      |     |
|   |        |                | CAG | CAG  | UAG   | UUG  | UCA  | ncn | GCU  | C   |
| 8 | 0      | H19A(+35+65)   | GCC | UGA  | GCU   | GAU  | CUG  | CUG | GCA  | ucu |
| 8 | 1      | H20A(+44+71)   | UGC |      |       |      |      |     |      |     |
| 8 | 2      | H20A(+147+168) | AGU | U    |       |      |      |     |      |     |
|   |        |                | CUG | GCA  | GAA   | UUC  | GAU  | CCA | CCG  | GCU |
|   |        |                | GUU | C    |       |      |      |     |      |     |
|   |        |                | CAG | CAG  | UAG   | UUG  | UCA  | ncn | GCU  | C   |

### TABLE 1B-continued

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Description of a cocktail of 2'-0-methyl phosphorothicate antisense oligonuclectides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

|    | ID  | SEQUENCE       | NUCLEOTIDE SEQUENCE (5'-3')    |
|----|-----|----------------|--------------------------------|
| 50 | 194 | H53D(+14-07)   | UAC UAA CCU UGG UUU CUG UGA    |
|    | 195 | H53A(+23+47)   | CUG AAG GUG UUC UUG UAC UUC AU |
|    | 196 | H53A(+150+175) | UGU AUA GGG ACC CUC CUU CCA UC |

### TABLE 1C

Description of a "weasel" of 2'-0-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

| SEQ | SEQUENCE        | NUCLEOTIDE SEQUENCE (5'-3')            |
|-----|-----------------|--|
| 81  | H20A(+44+71)-   | CUG GCA GAA UUC GAU CCA CCG GCU GUU C- |
| 82  | H20A (+147+168) | CAG CAG UAG UUG UCA UCU GCU C          |

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## TABLE 1C-continued

Description of a "weasel" of 2'-O-methyl phosphorothicate antisense cligonuclectides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

| SEG | SEQUENCE   | NUCLEOTIDE SEQUENCE (5'-3')                               |
|-----|--|---|
| 80  | H19A(+35+65)-  | GCC UGA GCU GAU CUG CUG GCA UCU UGC                       |
| 88  | H20A(+44+63) -   |   |
| 79  | H20A(+149+168)   | -AUU CGA UCC ACC GGC UGU UC-<br>CUG CUG GCA UCU UGC AGU U |
| 80  | H19A(+35+65) -   | GCC UGA GCU GAU CUG CUG GCA UCU UGC                       |
| 88  | H20A(+44+63)   | -AUU CGA UCC ACC GGC UGU UC-                              |
| 80  | H19A(+35+65) -   | GCC UGA GCU GAU CUG CUG GCA UCU UGC                       |
| 79  | H20A(+149+168)   | -CAG CAG GCY ACA ACA ACA A                                |
| 139 | H34A(+46+70)-  | CAU UCA UUU CCU UUC GCA UCU UAC G-                        |
| 139 | H34A(+94+120)  | UGA UCU CUU UGU CAA UUC CAU AUC UG                        |
|     | H31D(+03-22)-  | UAG UUU CUG AAA UAA CAU AUA CCU G-                        |
| 144 | H35A(+24+43)   | UCU UCA GGU GCA CCU UCU GU                                |
|     | H53A(+23+47) -<br>AA-  | CUG AAG GUG UUC UUG UAC UUC AUC C-                        |
| 196 | H53A(+150+175) -   | UGU ADA GGG ACC CUC CUU CCA UGA CUC-                      |
|     | A STATE OF THE STA | AA-<br>UAC UAA CCU UGG UUU CUG UGA                        |
| =   | Aimed at exons   | CAG CAG UAG UUG UCA UCU GCU CAA CUG                       |
| 12  | 19/20/20   | GCA GAA UUC GAU CCA CCG GCU GUU CAA                       |
|     |  | GCC UGA GCU GAU CUG CUC GCA UCU                           |
|     |  | UGC AGU   |

# DETAILED DESCRIPTION OF THE INVENTION

General

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variation and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally 50 equivalent products, compositions and methods are clearly within the scope of the invention as described herein.

Sequence identity numbers (SEQ ID NO:) containing nucleotide and amino acid sequence information included in this specification are collected at the end of the description 55 and have been prepared using the programme Patentln Version 3.0. Each nucleotide or amino acid sequence is identified in the sequence listing by the numeric indicator <210> followed by the sequence identifier (e.g. <210>1, <210>2, etc.). The length, type of sequence and source organism for each nucleotide or amino acid sequence are indicated by information provided in the numeric indicator fields <211>, <212> and <213>, respectively. Nucleotide and amino acid sequences referred to in the specification are defined by the information provided in numeric indicator 65 field <400> followed by the sequence identifier (e.g. <400>1, <400>2, etc.).

An antisense molecules nomenclature system was proposed and published to distinguish between the different antisense molecules (see Mann et al., (2002) *J Gen Med* 4, 644-654). This nomenclature became especially relevant when testing several slightly different antisense molecules, all directed at the same target region, as shown below:

H#A/D(x:y).

The first letter designates the species (e.g. H: human, M: murine, C: canine) "#" designates target dystrophin exon number.

"A/D" indicates acceptor or donor splice site at the beginning and end of the exon, respectively.

(x y) represents the annealing coordinates where "-" or "+" indicate intronic or exonic sequences respectively. As an example, A(-6+18) would indicate the last 6 bases of the intron preceding the target exon and the first 18 bases of the target exon. The closest splice site would be the acceptor so these coordinates would be preceded with an "A". Describing annealing coordinates at the donor splice site could be D(+2-18) where the last 2 exonic bases and the first 18 intronic bases correspond to the annealing site of the antisense molecule. Entirely exonic annealing coordinates that would be represented by A(+65+85), that is the site between the 65th and 85th nucleotide from the start of that exon.

The entire disclosures of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference. No admission is made that any of the references constitute prior art or are part of the common general knowledge of those working in the field to which this invention relates.

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As used necessarily herein the term "derived" and "derived from" shall be taken to indicate that a specific integer may be obtained from a particular source albeit not directly from that source.

Throughout this specification, unless the context requires o#herwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Other definitions for selected terms used herein may be 10 found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

Description of the Preferred Embodiment

When antisense molecule(s) are targeted to nucleotide sequences involved in splicing in exons within pre-mRNA sequences, normal splicing of the exon may be inhibited causing the splicing machinery to by-pass the entire mutated 20 exon from the mature mRNA. The concept of antisense oligonucleotide induced exon skipping is shown in FIG. 2. In many genes, deletion of an entire exon would lead to the production of a non-functional protein through the loss of important functional domains or the disruption of the read- 25 ing frame. In some proteins, however, it is possible to shorten the protein by deleting one or more exons, without disrupting the reading frame, from within the protein without seriously altering the biological activity of the protein. Typically, such proteins have a structural role and or possess 30 functional domains at their ends. The present invention describes antisense molecules capable of binding to specified dystrophin pre-mRNA targets and re-directing processing of that gene.

Antisense Molecules

According to a first aspect of the invention, there is provided antisense molecules capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules are preferably selected from the group 40 of compounds shown in Table 1A. There is also provided a combination or "cocktail" of two or more antisense oligonucleotides capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules in a 45 "cocktail" are preferably selected from the group of compounds shown in Table 1B. Alternatively, exon skipping may be induced by antisense oligonucleotides joined together "weasels" preferably selected from the group of compounds shown in Table 1C.

Designing antisense molecules to completely mask consensus splice sites may not necessarily generate any skipping of the targeted exon. Furthermore, the inventors have discovered that size or length of the antisense oligonucleotide itself is not always a primary factor when designing antisense molecules. With some targets such as exon 19, antisense oligonucleotides as short as 12 bases were able to induce exon skipping, albeit not as efficiently as longer (20-31 bases) oligonucleotides. In some other targets, such as murine dystrophin exon 23, antisense oligonucleotides only 17 residues long were able to induce more efficient skipping than another overlapping compound of 25 nucleotides.

The inventors have also discovered that there does not appear to be any standard motif that can be blocked or masked by antisense molecules to redirect splicing. In some exons, such as mouse dystrophin exon 23, the donor splice

site was the most amenable to target to re-direct skipping of that exon. It should be noted that designing and testing a series of exon 23 specific antisense molecules to anneal to overlapping regions of the donor splice site showed considerable variation in the efficacy of induced exon skipping. As reported in Mann et al., (2002) there was a significant variation in the efficiency of bypassing the nonsense mutation depending upon antisense oligonucleotide annealing ("Improved antisense oligonucleotide induced exon skipping in the mdx mouse model of muscular dystrophy". J Gen Med 4: 644-654). Targeting the acceptor site of exon 23 or several internal domains was not found to induce any

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consistent exon 23 skipping.

In other exons targeted for removal, masking the donor 15 splice site did not induce any exon skipping. However, by directing antisense molecules to the acceptor splice site (human exon 8 as discussed below), strong and sustained exon skipping was induced. It should be noted that removal of human exon 8 was tightly linked with the co-removal of exon 9. There is no strong sequence homology between the exon 8 antisense oligonucleotides and corresponding regions of exon 9 so it does not appear to be a matter of cross reaction. Rather the splicing of these two exons is inextricably linked. This is not an isolated instance as the same effect is observed in canine cells where targeting exon 8 for removal also resulted in the skipping of exon 9. Targeting exon 23 for removal in the mouse dystrophin pre-mRNA also results in the frequent removal of exon 22 as well. This effect occurs in a dose dependent manner and also indicates close coordinated processing of 2 adjacent exons.

In other targeted exons, antisense molecules directed at the donor or acceptor splice sites did not induce exon skipping while annealing antisense molecules to intra-exonic regions (i.e. exon splicing enhancers within human dystrophin exon 6) was most efficient at inducing exon skipping. Some exons, both mouse and human exon 19 for example, are readily skipped by targeting antisense molecules to a variety of motifs. That is, targeted exon skipping is induced after using antisense oligonucleotides to mask donor and acceptor splice sites or exon splicing enhancers.

To identify and select antisense oligonucleotides suitable for use in the modulation of exon skipping, a nucleic acid sequence whose function is to be modulated must first be identified. This may be, for example, a gene (or mRNA transcribed form the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (i.e. splice donor sites, splice acceptor sites, or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

Preferably, the present invention aims to provide antisense molecules capable of binding to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping. Duchenne muscular dystrophy arises from mutations that preclude the synthesis of a functional dystrophin gene product. These Duchenne muscular dystrophy gene defects are typically nonsense mutations or genomic rearrangements such as deletions, duplications or microdeletions or insertions that disrupt the reading frame. As the human dystrophin gene is a large and complex gene with the 79 exons being spliced together to generate a mature mRNA with an open reading frame of approximately 11,000 bases, there are many positions where these mutations can occur. Consequently, a comprehensive antisense oligonucleotide

based therapy to address many of the different diseasecausing mutations in the dystrophin gene will require that many exons can be targeted for removal during the splicing process.

Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (i.e. splice donor sites, splice acceptor sites or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

The oligonucleotide and the DNA or RNA are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides which can hydrogen bond with each other. Thus, "specifically hybridisable" and "complementary" are terms 15 which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an antisense molecule need not be 100% complementary to 20 that of its target sequence to be specifically hybridisable. An antisense molecule is specifically hybridisable when binding of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of utility, and there is a sufficient degree 25 of complementarity to avoid non-specific binding of the antisense compound to non-target sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of in vivo assays or therapeutic treatment, and in the case of in vitro assays, under 30 conditions in which the assays are performed.

While the above method may be used to select antisense molecules capable of deleting any exon from within a protein that is capable of being shortened without affecting its biological function, the exon deletion should not lead to 35 a reading frame shift in the shortened transcribed mRNA. Thus, if in a linear sequence of three exons the end of the first exon encodes two of three nucleotides in a codon and the next exon is deleted then the third exon in the linear sequence must start with a single nucleotide that is capable 40 of completing the nucleotide triplet for a codon. If the third exon does not commence with a single nucleotide there will be a reading frame shift that would lead to the generation of truncated or a non-functional protein.

It wilt be appreciated that the codon arrangements at the 45 end of exons in structural proteins may not always break at the end of a codon, consequently there may be a need to delete more than one exon from the pre-mRNA to ensure in-frame reading of the mRNA. In such circumstances, a plurality of antisense oligonucleotides may need to be 50 selected by the method of the invention wherein each is directed to a different region responsible for inducing splic-

ing in the exons that are to be deleted.

The length of an antisense molecule may vary so long as it is capable of binding selectively to the intended location 55 within the pre-mRNA molecule. The length of such sequences can be determined in accordance with selection procedures described herein. Generally, the antisense molecule will be from about 10 nucleotides in length up to about 50 nucleotides in length. It will be appreciated however that 60 any length of nucleotides within this range may be used in the method. Preferably, the length of the antisense molecule is between 17 to 30 nucleotides in length.

In order to determine which exons can be connected in a dystrophin gene, reference should be made to an exon 65 boundary map. Connection of one exon with another is based on the exons possessing the same number at the 3'

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border as is present at the 5' border of the exon to which it is being connected. Therefore, if exon 7 were deleted, exon 6 must connect to either exons 12 or 18 to maintain the reading frame. Thus, antisense oligonucleotides would need to be selected which redirected splicing for exons 7 to 11 in the first instance or exons 7 to 17 in the second instance. Another and somewhat simpler approach to restore the reading frame around an exon 7 deletion would be to remove the two flanking exons. Induction of exons 6 and 8 skipping should result in an in-frame transcript with the splicing of exons 5 to 9. In practise however, targeting exon 8 for removal from the pre-mRNA results in the co-removal of exon 9 so the resultant transcript would have exon 5 joined to exon 10. The inclusion or exclusion of exon 9 does not alter the reading frame. Once the antisense molecules to be tested have been identified, they are prepared according to standard techniques known in the art. The most common method for producing antisense molecules is the methylation of the 2' hydroxyribose position and the incorporation of a phosphorothioate backbone produces molecules that superficially resemble RNA but that are much more resistant to nuclease degradation.

To avoid degradation of pre-mRNA during duplex formation with the antisense molecules, the antisense molecules used in the method may be adapted to minimise or prevent cleavage by endogenous RNase H. This property is highly preferred as the treatment of the RNA with the unmethylated oligonucleotides either intracellularly or in crude extracts that contain RNase H leads to degradation of the pre-mRNA: antisense oligonucleotide duplexes. Any form of modified antisense molecules that is capable of bypassing or not inducing such degradation may be used in the present method. An example of antisense molecules which when duplexed with RNA are not cleaved by cellular RNase H is 2'-O-methyl derivatives, 2'-O-methyl-oligoribonucleotides are very stable in a cellular environment and in animal tissues, and their duplexes with RNA have higher Tm values than their ribo- or deoxyribo-counterparts.

Antisense molecules that do not activate RNase H can be made in accordance with known techniques (see, e.g., U.S. Pat. No. 5,149,797). Such antisense molecules, which may be deoxyribonucleotide or ribonucleotide sequences, simply contain any structural modification which sterically hinders or prevents binding of RNase H to a duplex molecule containing the oligonucleotide as one member thereof, which structural modification does not substantially hinder or disrupt duplex formation. Because the portions of the oligonucleotide involved in duplex formation are substantially different from those portions involved in RNase H binding thereto, numerous antisense molecules that do not activate RNase H are available. For example, such antisense molecules may be oligonucleotides wherein at least one, or all, of the inter-nucleotide bridging phosphate residues are modified phosphates, such as methyl phosphonates, methyl phosphorothioates, phosphoromorpholidates, phosphoropiperazidates and phosphoramidates. For example, every other one of the internucleotide bridging phosphate residues may be modified as described. In another non-limiting example, such antisense molecules are molecules wherein at least one, or all, of the nucleotides contain a 2' lower alkyl moiety (e.g., C1-C4, linear or branched, saturated or unsaturated alkyl, such as methyl, ethyl, ethenyl, propyl, 1-propenyl. 2-propenyl, and isopropyl). For example, every other one of the nucleotides may be modified as described.

While antisense oligonucleotides are a preferred form of the antisense molecules, the present invention comprehends

other oligomeric antisense molecules, including but not limited to oligonucleotide mimetics such as are described

Specific examples of preferred antisense compounds useful in this invention include oligonucleotides containing 5 modified backbones or non-natural inter-nucleoside linkages. As defined in this specification, oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this 10 specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their inter-nucleoside backbone can also be considered to be oligonucleosides.

In other preferred oligonucleotide mimetics, both the 15 sugar and the inter-nucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown 20 to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugarbackbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleo-bases are retained and are bound 25 directly or indirectly to aza nitrogen atoms of the amide portion of the backbone.

Modified oligonucleotides may also contain one or more substituted sugar moieties. Oligonucleotides may also include nucleobase (often referred to in the art simply as 30 "base") modifications or substitutions. Certain nucleo-bases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropylad- 35 enine, 5-propynyluracil and 5-propynylcytosine, 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2° C. and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. Such moieties include but are not limited to lipid 45 compound is administered. Such pharmaceutical carriers can moieties such as a cholesterol moiety, cholic acid. a thioether, e.g., hexyl-S-tritylthiol, a thiocholesterol, an aliphatic chain, e.g., dodecandiol or undecyl residues, a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or 50 a polyethylene glycol chain, or adamantane acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety.

It is not necessary far all positions in a given compound to be uniformly modified, and in fact more than one of the 55 aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes antisense compounds that are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this 60 invention, are antisense molecules, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region 65 wherein the oligonucleotide is modified so as to confer upon the increased resistance to nuclease degradation, increased

28 cellular uptake, and an additional region for increased binding affinity for the target nucleic acid.

Methods of Manufacturing Antisense Molecules

The antisense molecules used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). One method for synthesising oligonucleotides on a modified solid support is described in U.S. Pat. No. 4,458,066.

Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates ~ and alkylated derivatives. In one such automated embodiment, diethyl-phosphoramidites are used as starting materials and may be synthesized as described by Beaucage, et al., (1981) Tetrahedron Letters, 22:1859-1862.

The antisense molecules of the invention are synthesised in vitro and do not include antisense compositions of biological origin, or genetic vector constructs designed to direct the in vivo synthesis of antisense molecules. The molecules of the invention may also be mixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption.

Therapeutic Agents

The present invention also can be used as a prophylactic or therapeutic, which may be utilised for the purpose of treatment of a genetic disease.

Accordingly, in one embodiment the present invention provides antisense molecules that bind to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping described herein in a therapeutically effective amount admixed with a pharmaceutically acceptable carrier, diluent, or excipient.

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic or similarly untoward reaction, such as gastric upset and the like, when administered to a patient. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in Martin, Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, Pa., (1990).

In a more specific form of the invention there are provided pharmaceutical compositions comprising therapeutically effective amounts of an antisense molecule together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength and additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol). The material may be incorporated into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hylauronic

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acid may also be used. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Martin, *Remington's Pharmaceutical Sciences*, 18th Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 51435-1712 that are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilised form.

It will be appreciated that pharmaceutical compositions provided according to the present invention may be administered by any means known in the art. Preferably, the pharmaceutical compositions for administration are administered by injection, orally, or by the pulmonary, or nasal route. The antisense molecules are more preferably delivered by intravenous, intra-arterial, intraperitoneal, intramuscular, or subcutaneous routes of administration.

Antisense Molecule Based Therapy

Also addressed by the present invention is the use of antisense molecules of the present invention, for manufacture of a medicament for modulation of a genetic disease. 20

The delivery of a therapeutically useful amount of antisense molecules may be achieved by methods previously published. For example, intracellular delivery of the antisense molecule may be via a composition comprising an admixture of the antisense molecule and an effective amount of a block copolymer. An example of this method is described in US patent application US 20040248833.

Other methods of delivery of antisense molecules to the nucleus are described in Mann C J et al., (2001) ["Antisense-induced exon skipping and the synthesis of dystrophin in the 30 mdx mouse". Proc., Natl. Acad. Science, 98(1) 42-47J and in Gebski et al., (2003). Human Molecular Genetics, 12(15): 1801-1811.

A method for introducing a nucleic acid molecule into a cell by way of an expression vector either as naked DNA or 35 complexed to lipid carriers, is described in U.S. Pat. No. 6.806,084.

It may be desirable to deliver the antisense molecule in a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, micro-40 spheres, beads, and lipid-based systems including oil-inwater emulsions, micelles, mixed micelles, and liposomes or liposome formulations.

Liposomes are artificial membrane vesicles which are useful as delivery vehicles in vitro and in vivo. These 45 formulations may have net cationic, anionic or neutral charge characteristics and are useful characteristics with in vitro, in vivo and ex vivo delivery methods. It has been shown that large unilamellar vesicles (LUV), which range in size from 0.2-4.0.PHI.m can encapsulate a substantial percentage of an aqueous buffer containing large macromolecules. RNA, and DNA can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, et al., Trends Biochem. Sci., 6:77, 1981).

In order for a liposome to be an efficient gene transfer 55 vehicle, the following characteristics should be present: (1) encapsulation of the antisense molecule of interest at high efficiency while not compromising their biological activity; (2) preferential and substantial binding to a target cell in comparison to non-target cells; (3) delivery of the aqueous contents of the vesicle to the target cell cytoplasm at high efficiency; and (4) accurate and effective expression of genetic information (Mannino, et al., Biotechniques, 6:682, 1988)

The composition of the liposome is usually a combination 65 of phospholipids, particularly high-phase-transition-temperature phospholipids, usually in combination with ste-

roids, especially cholesterol. Other phospholipids or other lipids may also be used. The physical characteristics of liposomes depend on pH, ionic strength, and the presence of divalent cations.

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Alternatively, the antisense construct may be combined with other pharmaceutically acceptable carriers or diluents to produce a pharmaceutical composition. Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. The composition may be formulated for parenteral, intramuscular, intravenous, subcutaneous, intraocular, oral or transdermal administration.

The routes of administration described are intended only as a guide since a skilled practitioner will be able to determine readily the optimum route of administration and any dosage for any particular animal and condition. Multiple approaches for introducing functional new genetic material into cells, both in vitro and in vivo have been attempted (Friedmann (1989) Science, 244:1275-1280).

These approaches include integration of the gene to be expressed into modified retroviruses (Friedmann (1989) supra; Rosenberg (1991) Cancer Research 51(18), suppl.: 5074S-5079S); integration into non-retrovirus vectors (Rosenfeld, et al. (1992) Cell, 68:143-155; Rosenfeld, et al. (1991) Science, 252:431-434); or delivery of a transgene linked to a heterologous promoter-enhancer element via liposomes (Friedmann (1989), supra; Brigham, et al. (1989) Am. J. Med. Sci., 298:278-281; Nabel, et al. (1990) Science, 249:1285-1288; Hazinski, et al. (1991) Am. J. Resp. Cell Molec. Biol., 4:206-209; and Wang and Huang (1987) Proc. Natl. Acad. Sci. (USA), 84:7851-7855); coupled to ligandspecific, cation-based transport systems (Wu and Wu (1988) J. Biol. Chem., 263:14621-14624) or the use of naked DNA. expression vectors (Nabel et al. (1990), supra); Wolff et al. (1990) Science, 247:1465-1468). Direct injection of transgenes into tissue produces only localized expression (Rosenfeld (1992) supra); Rosenfeld et al. (1991) supra; Brigham et al. (1989) supra; Nabel (1990) supra; and Hazinski et al. (1991) supra). The Brigham et al. group (Am. J. Med. Sci. (1989) 298:278-281 and Clinical Research (1991) 39 (abstract)) have reported in vivo transfection only of lungs of mice following either intravenous or intratracheal administration of a DNA liposome complex. An example of a review article of human gene therapy procedures is: Anderson, Science (1992) 256:808-813.

The antisense molecules of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to prodrugs and pharmaceutically acceptable salts of the compounds of the invention, pharmaceutically acceptable salts of such pro-drugs, and other bioequivalents.

The term "pharmaceutically acceptable salts" refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

For oligonucleotides, preferred examples of pharmaceutically acceptable salts include but are not limited to (a) salts formed with cations such as sodium, potassium, ammonium, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, malefic

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acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polygiutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine. The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may to be topical (including ophthalmic and to mucous membranes including rectal delivery), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, (including by nebulizer, intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, 15 intra-arterial, subcutaneous, intraperitoneal or intramuscular injection or infusion: or intracranial, e.g., intrathecal or intraventricular, administration. Oligonucleotides with at least one 2'-O-methoxyethyl modification are believed to be particularly useful for oral administration.

The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active 25 ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

30 Kits of the Invention

The invention also provides kits for treatment of a patient with a genetic disease which kit comprises at least an antisense molecule, packaged in a suitable container, together with instructions for its use.

In a preferred embodiment, the kits will contain at least one antisense molecule as shown in Table 1A, or a cocktail of antisense molecules as shown in Table 1B or a "weasel" compound as shown in Table 1C. The kits may also contain peripheral reagents such as buffers, stabilizers, etc.

Those of ordinary skill in the field should appreciate that applications of the above method has wide application for identifying antisense molecules suitable for use in the treatment of many other diseases.

### EXAMPLES

The following Examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out 50 various aspects of the invention. It is understood that these Examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. The references cited herein are expressly incorporated by reference.

Methods of molecular cloning, immunology and protein chemistry, which are not explicitly described in the following examples, are reported in the literature and are known by those skilled in the art. General texts that described conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art, included, for example; Sambrook et al, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989); Glover ed., *DNA Cloning: A Practical Approach*, Volumes I and II, MRL 65 Press, Ltd., Oxford, U. K. (1985); and Ausubel, F., Brent, R., Kingston, R. E., Moore, D. D., Seidman, J. G., Smith, J. A.,

Struhl, K. Current Protocols in Molecular Biology. Greene

Publishing Associates/Wiley Intersciences, New York (2002).

### Determining Induced Exon Skipping in Human Muscle Cells

Attempts by the inventors to develop a rational approach in antisense molecules design were not completely successful as there did not appear to be a consistent trend that could be applied to all exons. As such, the identification of the most effective and therefore most therapeutic antisense molecules compounds has been the result of empirical studies.

These empirical studies involved the use of computer programs to identify motifs potentially involved in the splicing process. Other computer programs were also used to identify regions of the pre-mRNA which may not have had extensive secondary structure and therefore potential sites for annealing of antisense molecules. Neither of these approaches proved completely reliable in designing antisense oligonucleotides for reliable and efficient induction of exon skipping.

Annealing sites on the human dystrophin pre-mRNA were selected for examination, initially based upon known or predicted motifs or regions involved in splicing. 20Me antisense oligonucleotides were designed to be complementary to the target sequences under investigation and were synthesised on an Expedite 8909 Nucleic Acid Synthesiser. Upon completion of synthesis, the oligonucleotides were cleaved from the support column and de-protected in ammonium hydroxide before being desalted. The quality of the oligonucleotide synthesis was monitored by the intensity of the trityl signals upon each deprotection step during the synthesis as detected in the synthesis log. The concentration of the antisense oligonucleotide was estimated by measuring the absorbance of a diluted aliquot at 260 nm.

Specified amounts of the antisense molecules were then tested for their ability to induce exon skipping in an in vitro assay, as described below.

Briefly, normal primary myoblast cultures were prepared from human muscle biopsies obtained after informed consent. The cells were propagated and allowed to differentiate into myotubes using standard culturing techniques. The cells were then transfected with the antisense oligonucleotides by delivery of the oligonucleotides to the dells as cationic lipoplexes, mixtures of antisense molecules or cationic liposome preparations.

The cells were then allowed to grow for another 24 hours, after which total RNA was extracted and molecular analysis commenced. Reverse transcriptase amplification (RT-PCR) was undertaken to study the targeted regions of the dystrophin pre-mRNA or induced exonic re-arrangements.

For example, in the testing of an antisense molecule for inducing exon 19 skipping the RT-PCR test scanned several exons to detect involvement of any adjacent exons. For example, when inducing skipping of exon 19, RT-PCR was carried out with primers that amplified across exons 17 and 21. Amplifications of even larger products in this area (i.e. exons 13-26) were also carried out to ensure that there was minimal amplification bias for the shorter induced skipped transcript. Shorter or exon skipped products tend to be amplified more efficiently and may bias the estimated of the normal and induced transcript.

The sizes of the amplification reaction products were estimated on an agarose gel and compared against appropriate size standards. The final confirmation of identity of

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these products was carried out by direct DNA sequencing to establish that the correct or expected exon junctions have been maintained.

Once efficient exon skipping had been induced with one antisense molecule, subsequent overlapping antisense molecules may be synthesized and then evaluated in the assay as described above. Our definition of an efficient antisense molecule is one that induces strong and sustained exon skipping at transfection concentrations in the order of 300 nM or less.

# Antisense Oligonucleotides Directed at Exon 8

Antisense oligonucleotides directed at exon 8 were prepared and tested for their ability to induce exon skipping in 15 human muscle cells using similar methods as described above.

FIG. 3 shows differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. H8A(-06+18)

shown that targeting of the antisense molecules to motifs involved in the splicing process plays a crucial role in the overall efficacy of that compound.

Efficacy refers to the ability to induce consistent skipping of a target exon. However, sometimes skipping of the target exons is consistently associated with a flanking exon. That is, we have found that the splicing of some exons is tightly linked. For example, in targeting exon 23 in the mouse model of muscular dystrophy with antisense molecules directed at the donor site of that exon, dystrophin transcripts missing exons 22 and 23 are frequently detected. As another example, when using an antisense molecule directed to exon 8 of the human dystrophin gene, all induced transcripts are missing both exons 8 and 9. Dystrophin transcripts missing only exon 8 are not observed.

Table 2 below discloses antisense molecule sequences that induce exon 8 (and 9) skipping.

#### TABLE 2

| SEQ ID | Antisense<br>Oligonucleotide<br>name | Sequence                                | Ability to induce skipping        |
|--------|--------------------------------------|---|-----------------------------------|
| 1      | H8A(-06+18)                          | 5'-GAU AGG UGG UAU CAA<br>CAU CUG UAA   | Very strong to 20 nM              |
| 2      | H8A (-03+18)                         | 5'-GAU AGG UGG UAU CAA<br>CAU CUG       | Very strong<br>skipping to 40 nM  |
| 3      | H8A (-07+18)                         | 5'-GAU AGG UGG UAU CAA<br>CAU CUG UAA G | Strong skipping to                |
| 4      | H8A(-06+14)                          | 5'-GGU GGU AUC AAC AUC<br>UGU AA        | Skipping to<br>300 nM             |
| 5      | H8A(-10+10)                          | 5'-GUA UCA ACA UCU GUA<br>AGC AC        | Patchy/weak<br>skipping to 100 nm |

[SEQ ID NO:1], which anneals to the last 6 bases of intron 7 and the first 18 bases of exon 8, induces substantial exon 8 and 9 skipping when delivered into cells at a concentration of 20 nM. The shorter antisense molecule, H8A(-06+14) [SEQ ID NO: 4] was only able to induce exon 8 and 9 skipping at 300 nM, a concentration some 15 fold higher than H8A(-06+18), which is the preferred antisense molecule.

This data shows that some particular antisense molecules induce efficient exon skipping while another antisense molecule, which targets a near-by or overlapping region, can be much less efficient. Titration studies show one compound is able to induce targeted exon skipping at 20 nM while the less efficient antisense molecules only induced exon skipping at concentrations of 300 nM and above. Therefore, we have

### Antisense Oligonucleotides Directed at Exon 7

Antisense oligonucleotides directed at exon 7 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 4 shows the preferred antisense molecule, H7A(+ 45+67) [SEQ ID NO: 6], and another antisense molecule, H7A(+2+26) [SEQ ID NO: 7], inducing exon 7 skipping. Nested amplification products span exons 3 to 9. Additional products above the induced transcript missing exon 7 arise from amplification from carry-over outer primers from the RT-PCR as well as heteroduplex formation.

Table 3 below discloses antisense molecule sequences for induced exon 7 skipping.

TABLE 3

|   | Antisense<br>Oligonucleotide<br>name | Sequence                                  | Ability to induce skipping  |
|---|--------------------------------------|---|-----------------------------|
| 6 | H7A(+45+67)                          | 5' - UGC AUG UUC CAG UCG UUG UGU<br>GG    | Strong skipping<br>to 20 nM |
| 7 | H7A(+02+26)                          | 5' - CAC UAU UCC AGU CAA AUA GGU<br>CUG G | Weak skipping at            |

300 nM

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|   | Antisense<br>Oligonucleotide<br>name | Sequence                                 | Abdita                     |
|---|--------------------------------------|--|----------------------------|
| 8 | H7D(+15-10)                          |  | Ability to induce skipping |
| Ĭ |                                      | 5' -AUU UAC CAA CCU UCA GGA UCG<br>AGU A | Weak skipping to           |
| 9 | H7A(-18+03)                          | 5' - GGC CUA AAA CAC AUA CAC AUA         | Weak skipping to           |

# Antisense Oligonucleotides Directed at Exon 6

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Antisense oligonucleotides directed at exon 6 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 5 shows an example of two non-preferred antisense molecules inducing very low levels of exon 6 skipping in cultured human cells. Targeting this exon for specific removal was first undertaken during a study of the canine model using the oligonucleotides as listed in Table 4, below. Some of the human specific oligonucleotides were also evaluated, as shown in FIG. 5. In this example, both antisense molecules target the donor splice site and only induced low levels of exon 6 skipping. Both H6D(+4-21) [SEQ ID NO: 17] and H6D(+18-4) [SEQ ID NO: 18] would be regarded as non-preferred antisense molecules.

One antisense oligonucleotide that induced very efficient exon 6 skipping in the canine model, C6A(+69+91) [SEQ ID NO: 14], would anneal perfectly to the corresponding region in human dystrophin exon 6. This compound was evaluated, found to be highly efficient at inducing skipping of that target exon, as shown in FIG. 6 and is regarded as the preferred compound for induced exon 6 skipping. Table 4 below discloses antisense molecule sequences for induced exon 6 skipping.

### Antisense Oligonucleotides Directed at Exon 4

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Antisense oligonucleotides directed at exon 4 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 7 shows an example of a preferred antisense molecule inducing skipping of exon 4 skipping in cultured human cells. In this example, one preferred antisense compound, H4A(+13+32) [SEQ ID NO:19], which targeted a presumed exonic splicing enhancer induced efficient exon skipping at a concentration of 20 nM while other nonpreferred antisense oligonucleotides failed to induce even low levels of exon 4 skipping. Another preferred antisense molecule inducing skipping of exon 4 was H4A(+111+40) [SEQ ID NO:22], which induced efficient exon skipping at a concentration of 20 nM.

Table 5 below discloses antisense molecule sequences for inducing exon 4 skipping.

TABLE 4

| SEQ ID | Antisense Oligo<br>name | Sequence                                 | Ability to induce skipping      |
|--------|-------------------------|--|---------------------------------|
| 10     | C6A(-10+10)             | 5' CAU UUU UGA CCU ACA UGU<br>GG         | No skipping                     |
| 11     | C6A(-14+06)             | 5' UUU GAC CUA CAU GUG GAA<br>AG         | No skipping                     |
| 12     | C6A(-14+12)             | 5' UAC AUU UUU GAC CUA CAU<br>GUG GAA AG | No skipping                     |
| 13     | C6A(~13+09)             | 5' AUU UUU GAC CUA CAU GGG<br>AAA G      | No skipping                     |
| 14     | CH6A(+69+91)            | 5' UAC GAG UUG AUU GUC GGA<br>CCC AG     | Strong skipping to 2 nM         |
| 15     | C6D(+12-13)             | 5' GUG GUC UCC UUA CCU AUG<br>ACU GUG G  | Weak skipping at 300 nM         |
| 16     | C6D(+06-11)             | 5' GGU CUC CUU ACC UAU GA                | No skipping                     |
| 17     | H6D(+04-21)             | 5' DGU CUC AGU AAU CUU CUU<br>ACC UAU    | Weak skipping to 50 nM          |
| 18     | H6D(+18-04)             | 5' UCU UAC CUA UGA CUA UGG<br>AUG AGA    | Very weak skipping to<br>300 nM |

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| ID | Antisense<br>Oligonucleotide name | Sec | quen         | ce  |     |     |     |      |     |     | Ability to induce |
|----|-----------------------------------|-----|--------------|-----|-----|-----|-----|------|-----|-----|-------------------|
| 19 | H4A(+13+32)                       | 51  | GCA          | UGA | acu | om  | -   | 7.43 | _   |     | skipping          |
|    |                                   |     |              |     |     |     |     |      |     |     | Skipping to       |
| 22 | H4A(+11+40)                       | AU  | ugu<br>c cut | UCA | GGG | CAU | GAA | cuc  | DUG | UGG | Skipping to       |
| 20 | H4D(+04-16)                       | 51  | CCA          | GGG | UAC | UAC | UUA | CAU  | UA  |     | No skipping       |
| 21 | H4D(-24-44)                       | 51  | AUC          | GUG | UGU | CAC | AGC | AUC  | CAG |     | No skipping       |

# Antisense Oligonucleotides Directed at Exon 3

Antisense oligonucleotides directed at exon 3 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

H3A(+30+60) [SEQ ID NO:23] induced substantial exon 3 skipping when delivered into cells at a concentration of 20 nM to 600 nM. The antisense molecule, H3A(+35+65) [SEQ ID NO: 24] induced exon skipping at 300 nM.

Table 6 below discloses antisense molecule sequences that induce exon 3 skipping.

TABLE 6

| SEQ ID | Antisense<br>Oligonucleotide name | Seq       | иелс       | e   |     |     |      |       |     |   | Ability to<br>induce<br>skipping        |
|--------|-----------------------------------|-----------|------------|-----|-----|-----|------|-------|-----|---|---|
| 2.3    | H3A(+30+60)                       |           | GAG        |     | ccu | ccc | AUC  | cug   | UAG | ŕ | Moderate<br>skipping to<br>20 to 600 nM |
| 24     | H3A(+35+65)                       |           | UCU<br>AGG |     | AGG | CGC | CUC  | CCA   | ucc |   | Working to<br>300 nM                    |
| 25     | H3A(+30+54)                       | GCG       | CCU        | ccc | AUC | CUG | UAG  | GUC   | ACU | G | Moderate<br>100-600 nM                  |
| 26     | H3D(+46-21)                       | nc<br>can | CGA        | GGA | GGU | CUA | GGA  | GGC   | GCC |   | No skipping                             |
| 27     | H3A(+30+50)                       | cuc       | CCA        | UCC | UGU | AGG | UCA  | CUG   |     |   | Moderate 20-<br>600 nM                  |
| 28     | H3D(+19-03)                       | UAC       | CAG        | עעע | UUG | ccc | UGU  | CAG   | G   |   | No skipping                             |
| 29     | H3A(-06+20)                       | UCA<br>AA | AUA        | UGC | UGC | UUC | CCA. | AAC I | JGA |   | No skipping                             |
| 30     | H3A(+37+61)                       | CUA       | GGA        | GGC | GCC | ncc | CAU  | ccu   | GUA | G | No skipping                             |

## Antisense Oligonucleotides Directed at Exon 5

Antisense oligonucleotides directed at exon 5 were prepared and tested for their ability to induce exon skipping in 55 human muscle cells using similar methods as described

H5A(+20+50) [SEQ ID NO:31] induces substantial exon 5 skipping when delivered into cells at a concentration of

100 nM. Table 7 below shows other antisense molecules tested. The majority of these antisense molecules were not as effective at exon skipping as H5A(+20+50). However, H5A (+15+45) [SEQ ID NO: 40] was able to induce exon 5 skipping at 300 nM.

Table 7 below discloses antisense molecule sequences that induce exon 5 skipping.

#### TABLE 7

| SEQ ID | Antisense<br>Oligonucleotide<br>name | Sequence                                    | Ability to<br>induce<br>skipping |
|--------|--------------------------------------|---|----------------------------------|
| 31     | H5A(+20+50)                          | UUA UGA UUU CCA UCU AC<br>AUG UCA GUA CUU C | G Working to<br>100 nM           |

No skipping

Working to

300 nM

55

39

SEQ

32

33

34

35 36 37

38

H5A(+05+35)

H5A(+15+45)

| ID | Antisense<br>Oligonucleotide<br>name | Sequence                                     | Ability to<br>induce<br>skipping |
|----|--------------------------------------|--|----------------------------------|
| 2  | H5D(+25-05)                          | CUU ACC UGC CAG UGG AGG<br>AUU AUA UUC CAA A |                                  |
| 3  | H5D(+10-15)                          | CAU CAG GAU UCU UAC CUG                      | Inconsistent                     |
| 1  | H5A(+10+34)                          | CGA UGU CAG UAC UUC CAA<br>UAU UCA C         |                                  |
| ,  | H5D(-04-21)                          | ACC AUU CAU CAG GAU UCU                      | No skipping                      |
|    | H5D(+16-02)                          | ACC UGC CAG UGG AGG AUU                      |                                  |
|    | H5A(-07+20)                          | CCA AUA UUC ACU AAA UCA<br>ACC UGU UAA       |                                  |
|    | H5D(+18-12)                          | CAG GAU UCU UAC CUG CCA<br>GUG GAG GAU UAU   | No skipping                      |
|    |                                      |  |                                  |

Antisense Oligonucleotides Directed at Exon 10

Antisense oligonucleotides directed at exon 10 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H10A(-05+16) [SEQ ID NO:41] induced substantial exon 10 skipping when delivered into cells. Table 8 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was variable. Table 8 below discloses antisense molecule sequences that induce exon 10 skipping.

TABLE 8

ACG AUG UCA GUA CUU CCA

AUU UCC AUC UAC GAU GUC

AUA UUC ACU AAA U

AGU ACU UCC AAU A

|    | Antisense<br>Oligonucleotide name | Seq | uenc | e   |     |     |     |       |     | lity to<br>uce skipping |
|----|-----------------------------------|-----|------|-----|-----|-----|-----|-------|-----|-------------------------|
| 41 | H10A(-05+16)                      | CAG | GAG  | cuu | CCA | AAU | GCU | GCA   | Not | tested                  |
| 42 | H10A(-05+24)                      | CUU | GUC  |     | AGG | AGC | uuc | CAA   | Not | tested                  |
| 43 | H10A(+98+119)                     | ucc | UCA  | GCA | GAA | AGA | AGC | CAC G | Not | tested                  |
| 44 | H10A(+130+149)                    | UUA | GAA  | AUC | UCU | CCU | UGU | GC    | No  | skipping                |
| 45 | H10A(-33-14)                      | UAA | AUU  | GGG | UGU | UAC | ACA | AU    | No  | skipping                |

Antisense Oligonucleotides Directed at Exon 11

Antisense oligonucleotides directed at exon 11 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 8B shows an example of H11A(+75+97) [SEQ ID N0:49] antisense molecule inducing exon 11 skipping in cultured human cells. H11A(+75+97) induced substantial exon 11 skipping when delivered into cells at a concentration of 5 nM. Table 9 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was observed at 100 nM.

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|       | Antisense      | Sea   | uenc |     |     | _   | _   | _   |    | #: <b>5364</b>  |     |      |
|-------|----------------|-------|------|-----|-----|-----|-----|-----|----|-----------------|-----|------|
| _     |                |       | cene |     |     |     |     |     |    | Ability         | to  |      |
| 46    | H11D(+26+49)   | ccc   | UGA  | GGC | Arm | 235 | AUC | -   | _  | induce s        | kip | ping |
| Trans |                | 10.65 |      |     |     |     |     |     |    | Skipping<br>nM  | at  | 100  |
| 47    | H11D(+11-09)   | AGG   | ACU  | UAC | UUG | CUU | UGU | טט  |    | Skipping        | at  | 100  |
| 48    | H11A(+11B+140) | cuu   | GAA  | טטט | AGG | AGA | UUC | AUC | UG | Skipping        | at  | 100  |
| 19    | H11A(+75+97)   | CAU   | CUU  | CUG | AUA | AUU | UUC | CUG | UU | Skipping<br>nM  | at  | 100  |
| 46    | H11D(+26+49)   | CCC   | UGA  | GGC | AUU | ccc | AUC | UUG |    | Skipping<br>5nM | at  |      |

## Antisense Oligonucleotides Directed at Exon 12

Antisense oligonucleotides directed at exon 12 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H12A(+52+75) [SEQ ID NO:50] induced substantial 25 exon 12 skipping when delivered into cells at a concentration of 5 nM, as shown in FIG. 8A. Table 10 below shows other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The antisense molecules ability to induce exon skipping was variable.

TABLE 10

| SEQ<br>ID | Antisense<br>Oligonucleotide<br>name | Seq | uenc  | e         |            | Ability to<br>induce<br>skipping |
|-----------|--------------------------------------|-----|-------|-----------|------------|----------------------------------|
| 50        | H12A(+52+75)                         | UCU | UCU   | GUU       | UUU<br>UCA | Skipping<br>at 5 nM              |
| 51        | H12A(-10+10)                         |     | 70000 | UAA       | ACU        | Skipping                         |
| 52        | H12A(+11+30)                         | GAA | AAU   | UU<br>AGA | ncc        | at 100 nM                        |
|           | 1125(111430)                         |     | AAA   |           | VCC        | skipping                         |

#### Antisense Oligonucleotides Directed at Exon 13

Antisense oligonucleotides directed at exon 13 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described <sup>5</sup> above.

H13A(+77+100) [SEQ ID NO:53] induced substantial exon 13 skipping when delivered into cells at a concentration of 5 nM. Table 11 below includes two other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These other antisense molecules were unable to induce exon skipping.

TABLE 11

| SEQ<br>ID | Antisense<br>Oligonucleotide<br>name | Sequence                           | Ability to<br>induce<br>skipping |
|-----------|--------------------------------------|------------------------------------|----------------------------------|
| 53        | H13A(+77+100)                        | CAG CAG UUG CGU<br>GAU CUC CAC UAG | skipping<br>at 5 nM              |

#### TABLE 11-continued

| SEQ<br>ID | Antisense<br>Oligonucleotide<br>name | Sequence                                | Ability to<br>induce<br>skipping |
|-----------|--------------------------------------|---|----------------------------------|
| 54        | H13A(+55+75)                         | UUC AUC AAC UAC<br>CAC CAC CAU          | No<br>skipping                   |
| 55        | H13D(+06-19)                         | CUA AGC AAA AUA<br>AUC UGA CCU UAA<br>G | No<br>skipping                   |

#### Antisense Oligonucleotides Directed at Exon 14

Antisense oligonucleotides directed at exon 14 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H14A(+37+64) [SEQ ID NO:56] induced weak exon 14 skipping when delivered into cells at a concentration of 100 nM. Table 12 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

#### TABLE 12

| SEQ<br>ID | Antisense<br>Oligonucleotide<br>name | Seq        | uenc       | Ability to<br>induce<br>skipping |          |                       |
|-----------|--------------------------------------|------------|------------|----------------------------------|----------|-----------------------|
| 56        | H14A(+37+64)                         |            | AGC        | AAA<br>GGU                       |          | Skipping<br>at 100 nM |
| 57        | H14A(+14+35)                         |            |            | CAG                              | AUG<br>C | No<br>skipping        |
| 58        | H14A(+51+73)                         |            |            | UGU<br>GAA                       |          | No<br>skipping        |
| 59        | H14D(-02+18)                         |            | UGU<br>AGA | UCU                              | UCA      | No<br>skipping        |
| 60        | H14D(+14-10)                         | 10000      |            | ACA<br>CAG                       |          | No<br>skipping        |
| 61        | H14A(+61+80)                         | CAU<br>AUG |            | AGA<br>UG                        | AGG      | No<br>skipping        |
| 52        | H14A(-12+12)                         | AUC        |            | CAA<br>AAG                       | 7.5      | No<br>skipping        |

35

SEQ

ID

43

Antisense Oligonucleotides Directed at Exon 15

Antisense oligonucleotides directed at exon 15 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described 5

H15A(-12+19) [SEQ ID NO:63] and H15A(+48+71) [SEQ ID NO:64] induced substantial exon 15 skipping when delivered into cells at a concentration of 10 Nm, as shown in FIG. 9A. Table 13 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 Nm. These other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

| TAB | LE | 13 |
|-----|----|----|
|     |    |    |

| SEQ<br>ID<br>63 | Antisense<br>Oligonucleotide<br>name<br>H15A(-12+19) | Sequen                        | e                       | Ability to<br>induce<br>skipping |
|-----------------|--|-------------------------------|-------------------------|----------------------------------|
|                 |  | GCC AUG<br>AAA GGG<br>AGA CAG | CAC UAA<br>ACU GCA<br>U | Skipping<br>at 5 Nm              |
| 64              | H15A(+48+71)   |                               | AAG CCA<br>UGA AUC      | Skipping<br>at 5 Nm              |
| 65              | H15A(+08+28)   | AUG CAC                       | AAA GCC<br>UAA          | No<br>skipping                   |
| 63              | H15A(-12+19)   |                               | CAC UAA<br>ACU GCA<br>U | No<br>skipping                   |
| 6               | H15D(+17-08)   | GUA CAU<br>AGU UUU<br>C       |                         | No<br>skipping                   |

TABLE 14-continued

Sequence

Oligonucleotide

Ability to

induce

skipping

| 1)<br>en | 69       | H16A(-06+19)   | CUA GAU CCG CUU Skipping<br>UUA AAA CCU GUU at 25 nM<br>A |
|----------|----------|----------------|---|
| vn       | 70<br>10 | H16A(+87+109)  | CCG UCU UCU GGG Skipping<br>UCA CUG ACU UA at 100 nM      |
| le<br>d. | 71       | H16A(-07+19)   | CUA GAU CCG CUU No<br>UUA AAA CCU GUU skipping<br>AA      |
| 1        | 5 72     | H16A(-07+13)   | CCG CUU UUA AAA No<br>CCU GUU AA skipping                 |
|          | 73       | H16A(+12+37)   | UGG AUU GCU UUU Mo<br>UCU UUU CUA GAU skipping<br>CC      |
| 2        | 0 74     | H16A(+92+116)  | CAU GCU UCC GUC No<br>UUC UGG GUC ACU akipping<br>G       |
| 2        | 75<br>5  | H16A(+45+67)   | G AUC UUG UUU No<br>GAG UGA AUA CAG skipping<br>U         |
|          | 76       | H16A(+105+126) | GUU AUC CAG CCA No<br>UGC UUC CGU C skipping              |
| 3(       | 77       | H16D(+05-20)   | UGA UAA UUG GUA NO<br>UCA CUA ACC UGU skipping<br>G       |
|          | 78       | H16D(+12-11)   | GUA UCA CUA ACC No<br>UGU GCU GUA C skipping              |

Antisense Oligonucleotides Directed at Exon 16

Antisense oligonucleotides directed at exon 16 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H16A(-12+19) [SEQ ID NO:67] and H16A(-06+25) [SEQ ID NO:68] induced substantial exon 16 skipping when delivered into cells at a concentration of 10 nM, as shown in FIG. 9B. Table 14 below includes other antisense molecules tested. H16A(-06+19) [SEQ ID NO:69] and H16A(+87+109) [SEQ ID NO:70] were tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These two antisense molecules were able to induce exon skipping at 25 nM and 100 nM, respectively. Additional antisense molecules were tested at 100, 200 and 300 nM and did not result in any exon skipping.

TABLE 14

|     |                                      | * ** - * * * * * * * * * * * * * * * *          |                                  |
|-----|--------------------------------------|---|----------------------------------|
| SEQ | Antisense<br>Oligonucleotide<br>name | Sequence  | Ability to<br>induce<br>skipping |
| 67  | H16A(-12+19)                         | CUA GAU CCG CUU<br>UUA AAA CCU GUU<br>AAA ACA A | skipping<br>at 5 nM              |
| 68  | H16A(-06+25)                         | UCU UUU CUA GAU<br>CCG CUU UUA AAA<br>CCU GUU A | skipping<br>at 5 nM              |

Antisense Oligonucleotides Directed at Exon 19

Antisense oligonucleotides directed at exon 19 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H19A(+35+65) [SEQ ID NO:79] induced substantial exon 19 skipping when delivered into cells at a concentration of 10 nM. This antisense molecule also showed very strong exon skipping at concentrations of 25, 50, 100, 300 and 600 nM.

FIG. 10 illustrates exon 19 and 20 skipping using a "cocktail" of antisense oligonucleotides, as tested using gel electrophoresis. It is interesting to note that it was not easy to induce exon 20 skipping using single antisense oligonucleotides H20A(+44+71) [SEQ ID NO:81] or H20A(+149+170) [SEQ ID NO:82], as illustrated in sections 2 and 3 of the gel shown in FIG. 10. Whereas, a "cocktail" of antisense oligonucleotides was more efficient as can be seen in section 4 of FIG. 10 using a "cocktail" of antisense oligonucleotides H20A(+44+71) and H20A(+149+170). When the cocktail was used to target exon 19, skipping was even stronger (see section 5, FIG, 10).

FIG. 11 illustrates gel electrophoresis results of exon 19/20 skipping using "weasels" The "weasels" were effective in skipping exons 19 and 20 at concentrations of 25, 50, 100, 300 and 600 nM. A further "weasel" sequence is shown in the last row of Table 3C. This compound should give good results.

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Antisense Oligonucleotides Directed at Exon 20

Antisense oligonucleotides directed at exon 20 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described 5

None of the antisense oligonucleotides tested induced exon 20 skipping when delivered into cells at a concentration of 10, 25, 50, 300 or 600 nM (see Table 15). Antisense molecules H20A(-11+17) [SEQ ID NO:86] and H20D(+ 08-20) [SEQ ID NO:87] are yet to be tested.

However, a combination or "cocktail" of H20A(+44+71) [SEQ ID NO: 81] and H20(+149+170) [SEQ ID NO:82] in a ratio of 1:1, exhibited very strong exon skipping at a concentration of 100 nM and 600 nM. Further, a combination of antisense molecules H19A(+35+65) [SEQ ID NO:79], H20A(+44+71) [SEQ ID NO:81] and H20A(+149+ 170) [SEQ ID NO:82] in a ratio of 2:1:1, induced very strong exon skipping at a concentration ranging from 10 nM to 600

| SEQ<br>ID   | Antisense<br>Oligonucleotide<br>name             | Seq                      | uenc                     | e                |            | Ability to induce skipping |
|-------------|--|--------------------------|--------------------------|------------------|------------|----------------------------|
| 91          | H20A(+44+71)                                     |                          | CCA                      |                  | geo        | No<br>skipping             |
| 82          | H20A(+147+168)                                   |                          |                          | UAG              | UUG<br>C   | No<br>skipping             |
| 9.3         | H20A(+185+203)                                   |                          | UGG                      |                  | GGU        | No<br>skipping             |
| 34          | H20A(-08+17)                                     |                          |                          |                  | AAC<br>AAA | No<br>skipping             |
| 95          | H20A(+30+53)                                     |                          |                          |                  | CAG        | No<br>skipping             |
| 36          | H20A(-11+17)                                     |                          | CUC                      |                  |            | Not<br>tested<br>yet       |
| 7           | H20D(+08-20)                                     |                          | CUU                      |                  | GAG<br>UUA | Not<br>tested<br>yet       |
| 1 &         | H2OA(+44+71) &<br>H2OA(+147+168)                 |                          | CCA<br>C<br>CAG          | CCG              | GCU        | Very<br>strong<br>skipping |
| 0, 81<br>82 | H19A(+35+65);<br>H20A(+44+71);<br>H20A(+147+168) | CUG<br>UGC<br>CUG<br>GAU | CUG<br>AGU<br>GCA<br>CCA | GCA<br>U;<br>GAA | חמכ        | Very<br>strong<br>skipping |
|             |  | GUU<br>CAG<br>UCA        | CAG                      | UAG              | uug<br>C   |                            |

### Antisense Oligonucleotides Directed at Exon 21

Antisense oligonucleotides directed at exon 21 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

H21A(+85+108) [SEQ ID NO:92] and H21A(+85+106) [SEQ ID NO:91] induced exon 21 skipping when delivered 46

into cells at a concentration of 50 nM. Table 16 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping

TABLE 16

| SEQ<br>ID | Antisense<br>Oligonucleotide<br>name |      |      |     |     |            |  |
|-----------|--------------------------------------|------|------|-----|-----|------------|--|
| 90        | 90 H21A(-06+16)                      |      | ĠĠIJ | UGA | cuu | Skips at   |  |
|           |                                      | CAU  | CCU  | GUG | C   | 600 nM     |  |
| 91        | H21A(+85+106)                        | cug  | CAU  | CCA | GGA | Skips at   |  |
|           |                                      | ACA  | UGG  | GUC | C   | 50 nM      |  |
| 92        | H21A(+65+10B)                        | GUC  | UGC  | AUC | CAG | Skips at   |  |
|           |                                      | GAA  | CAU  | GGG | UC  | 50 nM      |  |
| 93        | H21A(+08+31)                         | GUU  | GAA  | GAU | CUG | Skips      |  |
|           |                                      | AUA  |      | GGU | UGA | faintly to |  |
| 94        | H21D(+18-07)                         | UAC  | UUA  | CUG | ucu | No         |  |
|           | Sand of Sec. 4.18                    | 1000 | GCU  | CUU | UCU | skipping   |  |

#### Antisense Oligonucleotides Directed at Exon 22

Antisense oligonucleotides directed at exon 22 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described 30 above.

FIG. 12 illustrates differing efficiencies of two antisense molecules directed at exon 22 acceptor splice site. H22A(+ 125+106) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO: 98] induce strong exon 22 skipping from 50 nM to 600 35 nM concentration.

H22A(+125+146) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO:98] induced exon 22 skipping when delivered into cells at a concentration of 50 nM. Table 17 below shows other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed a variable ability to induce exon skipping,

TABLE 17

| SEQ<br>ID | Antisense<br>oligonucleotide<br>name | Seq | uenc | Ability to<br>induce<br>skipping |     |           |
|-----------|--------------------------------------|-----|------|----------------------------------|-----|-----------|
| 95        | H22A(+22+45)                         | CAC | UCA  | UGG                              | UCU | No        |
|           |                                      | CCU | GAU  | AGC                              | GCA | akipping  |
| 96        | H22A(+125+146)                       | CUG | CAA  | unc                              | ccc | Skipping  |
|           | superior and services and            | GAG |      | CUG                              |     | to 50 nM  |
| 97        | H22A(+47+69)                         | ACU | GCU  | GGA                              | ccc | Skipping  |
|           |                                      | AUG | UCC  | UGA                              | UG  | to 300 nM |
| 98        | H22A(+B0+101)                        | CUA | AGU  | UGA                              | GGU | Skipping  |
| 701       | 444000                               |     | GAG  |                                  | 000 | to 50 nM  |
| 99        | H22D(+13-11)                         | UAU | UCA  | CAG                              | ACC | No        |
|           |                                      | UGC | AAU  | UCC                              | CC  | skipping  |

#### Antisense Oligonucleotides Directed at Exon 23

Antisense oligonucleotides directed at exon 23 were prepared and tested for their ability to induce exon skipping in 65 human muscle cells using similar methods as described above.

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Table 18 below shows antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed no ability to induce exon skipping or are yet to be tested.

TABLE 18

| SEQ<br>ID | Antisense<br>oligonucleotide<br>name | Sequence                                 | Ability to<br>induce<br>skipping |
|-----------|--------------------------------------|--|----------------------------------|
| 100       | H23A(+34+59)                         | ACA GUG GUG CUG<br>AGA UAG UAU AGG<br>CC | No<br>skipping                   |
| 101       | H23A(+18+39)                         | UAG GCC ACU UUG<br>UUG CUC UUG C         | No<br>Skipping                   |
| 102       | H23A(+72+90)                         | UUC AGA GGG CGC                          | No<br>Skipping                   |

Antisense Oligonucleotides Directed at Exon 24

Antisense oligonucleotides directed at exon 24 were prepared using similar methods as described above. Table 19 below outlines the antisense oligonucleotides directed at exon 24 that are yet to be tested for their ability to induce exon 24 skipping.

TABLE 19

| SEQ<br>ID | Antisense<br>oligonucleotide<br>name | Seq | uenc | 8   |     | Ability to<br>induce<br>skipping | 35 |
|-----------|--------------------------------------|-----|------|-----|-----|----------------------------------|----|
| 103       | H24A(+48+70)                         | GGG | CAG  | GCC | AUU | Needs                            |    |
|           |                                      | CCU | CCU  | UCA | GA  | testing                          |    |
| 104       | H24A(-02+22)                         | UCU | UCA  | GGG | טטט | Needs                            |    |
|           |                                      | GUA | UGU  | GAU | UCU | testing                          | 40 |

#### Antisense Oligonucleotides Directed at Exon 25

Antisense oligonucleotides directed at exon 25 were prepared using similar methods as described above. Table 20 below shows the antisense oligonucleotides directed at exon 25 that are yet to be tested for their ability to induce exon 25 skipping.

TABLE 20

| SEQ<br>ID | Antisense<br>oligonucleotide<br>name | Sequence                                  | Ability to<br>induce<br>skipping |  |
|-----------|--------------------------------------|---|----------------------------------|--|
| 105       | H25A(+9+36)                          | CUG GGC UGA AUU<br>GUC UGA AUA UCA<br>CUG | Needs<br>testing                 |  |
| 106       | H25A(+131+156)                       | CUG UUG GCA CAU<br>GUG AUC CCA CUG<br>AG  | Needs<br>testing                 |  |
| 107       | H25D(+16-D8)                         | GUC UAU ACC UGU<br>UGG CAC AUG UGA        | Needs<br>testing                 |  |

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Antisense Oligonucleotides Directed at Exon 26

Antisense oligonucleotides directed at exon 26 were prepared using similar methods as described above. Table 21 below outlines the antisense oligonucleotides directed at exon 26 that are yet to be tested for their ability to induce exon 26 skipping.

TABLE 21

| SEQ<br>ID | Antisense<br>oligonucleotide<br>name | Sequence                                 | Ability to<br>induce<br>skipping |
|-----------|--------------------------------------|--|----------------------------------|
| 108       | H26A(+132+156)                       | UGC UUU CUG UAA<br>UUC AUC UGG AGU<br>U  | Needs<br>testing                 |
| 109       | H26A(-07+19)                         | CCU CCU UUC UGG<br>CAU AGA CCU UCC<br>AC | Needs<br>testing                 |
| 110       | H26A(+68+92)                         | UGU GUC AUC CAU<br>UCG UGC AUC UCU<br>G  | Paint<br>skipping<br>at 600 nM   |

Antisense Oligonucleotides Directed at Exon 27

Antisense oligonucleotides directed at exon 27 were prepared using similar methods as described above. Table 22 below outlines the antisense oligonucleotides directed at exon 27 that are yet to be tested for their ability to induce exon 27 skipping.

TABLE 22

| SEQ<br>ID         | Antisense<br>oligonucleotide<br>name    | Sequence                          | Ability to<br>induce<br>skipping              |
|-------------------|---|-----------------------------------|---|
| 111 H27A(+82+106) | UUA AGG CCU CUU<br>GUG CUA CAG GUG<br>G | Needs<br>testing                  |   |
| 112               | H27A(-4+19)                             | GGG CCU CUU CUU<br>UAG CUC UCU GA | Faint<br>skipping<br>at 600 and<br>300 nM     |
| 113               | H27D(+19-03)                            | GAC UUC CAA AGU<br>CUU GCA UUU C  | v. strong<br>skipping<br>at 600 and<br>300 nM |

Antisense Oligonucleotides Directed at Exon 28

Antisense oligonucleotides directed at exon 28 were prepared using similar methods as described above. Table 23 below outlines the antisense oligonucleotides directed at exon 28 that are yet to be tested for their ability to induce exon 28 skipping.

TABLE 23

| SEQ | Antisense<br>oligonucleotide<br>name | Sequence                           | Ability to induce skipping          |
|-----|--------------------------------------|------------------------------------|-------------------------------------|
| 114 | H28A(-05+19)                         | GCC AAC AUG CCC<br>AAA CUU CCU AAG | v. strong<br>skipping<br>at 600 and |

49
TABLE 23-continued

|           | Antisense               |  |                                     |     |           | T                                    | ABLE 24                                 |   |
|-----------|-------------------------|--|-------------------------------------|-----|-----------|--------------------------------------|---|---|
| SEQ<br>ID | oligonucleotide<br>name | Sequence                                 | Ability to<br>induce<br>skipping    | . 5 | SEQ<br>ID | Antisense<br>oligonucleotide<br>name | Sequence                                | Ability to<br>induce<br>skipping              |
| 115       | H28A(+99+124)           | CAG AGA UUU CCU<br>CAG CUC CGC CAG<br>GA | Needs<br>testing                    |     | 117       | H29A(+57+81)                         | UCC GCC AUC UGU<br>UAG GGU CUG UGC<br>C | Needs<br>testing                              |
| 116       | H28D(+16-05)            | CUU ACA UCU AGC<br>ACC UCA GAG           | v. strong<br>skipping<br>at 600 and | 10  | 118       | H29A(+18+42)                         | AUU UGG GUU AUC<br>CUC UGA AUG UCG<br>C | v. strong<br>skipping<br>at 600 and<br>300 nM |
|           |                         |  | 300 nM                              | 1.5 | 119       | H29D(+17-05)                         | CAU ACC UCU UCA<br>UGU AGU UCC C        | v. strong<br>skipping<br>at 600 and<br>300 nM |

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### Antisense Oligonucleotides Directed at Exon 29

Antisense oligonucleotides directed at exon 29 were prepared using similar methods as described above. Table 24 below outlines the antisense oligonucleotides directed at exon 29 that are yet to be tested for their ability to induce exon 29 skipping.

#### Antisense Oligonucleotides Directed at Exon 30

50

Antisense oligonucleotides directed at exon 30 were prepared using similar methods as described above. Table 25 below outlines the antisense oligonucleotides directed at exon 30 that are yet to be tested for their ability to induce exon 30 skipping.

#### TABLE 25

| SEQ ID | Antisense<br>oligonucleotide<br>name | Sequence                              | Ability to induce skipping              |  |
|--------|--------------------------------------|---------------------------------------|---|--|
| 120    | H30A(+122+147)                       | CAU UUG AGC UGC GUC CAC               | Needs testing                           |  |
| 121    | H30A(+25+50)                         | UCC UGG GCA GAC UGG AUG<br>CUC UGU UC | Very strong skipping at 600 and 300 nM. |  |
| 122    | H30D(+19-04)                         | UUG CCU GGG CUU CCU GAG<br>GCA UU     | Very strong skipping at 600 and 300 nM. |  |

#### Antisense Oligonucleotides Directed at Exon 31

Antisense oligonucleotides directed at exon 31 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 13 illustrates differing efficiencies of two antisense molecules directed at exon 31 acceptor splice site and a "cocktail" of exon 31 antisense oligonucleotides at varying concentrations. H31D(+03-22) [SEQ ID NO:124] substantially induced exon 31 skipping when delivered into cells at a concentration of 20 nM. Table 26 below also includes other antisense molecules tested at a concentration of 100 and 300 nM.

These antisense molecules showed a variable ability to induce exon skipping.

#### TABLE 26

| SEQ ID | Antisense<br>oligonucleotide<br>name | Sequence                           | Ability to induce skipping |  |
|--------|--------------------------------------|------------------------------------|----------------------------|--|
| 123    | H31D(+06-18)                         | UUC UGA AAU AAC AUA UAC CUG<br>UGC | Skipping to 300 nM         |  |
| 124    | H31D(+03-22)                         | UAG UUU CUG AAA UAA CAU AUA        | Skipping to 20 nM          |  |

No skipping

Skipping to 300 nM

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GUU UCU GAA AUA ACA UAU ACC

TABLE 26-continued oligonucleotide Sequence Ability to induce skipping GAC UUG UCA AAU CAG AUU GGA

## Antisense Oligonucleotides Directed at Exon 32

51

Antisense

H31A(+05+25)

H31D(+04-20)

SEQ ID

125

126

Antisense oligonucleotides directed at exon 32 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H32D(+04-16) [SEQ ID NO:127] and H32A(+49+73) [SEQ ID NO:130] induced exon 32 skipping when delivered into cells at a concentration of 300 nM. Table 27 below also shows other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules did not show an ability to induce exon skipping.

#### TABLE 27

| SEQ ID | Antisense<br>oligonucleotide<br>name | Sequer | ice   |     | Ability to induce skipping |     |     |                    |
|--------|--------------------------------------|--------|-------|-----|----------------------------|-----|-----|--------------------|
| 127    | H32D(+04+16)                         | CAC CA | G AAA | UAC | AUA                        | CCA | CA  | Skipping to 300 nM |
| 128    | H32A(+151+170)                       | CAA U  | UUU A | AGC | UGU                        | GAC | UG  | No skipping        |
| 129    | H32A(10+32)                          | CGA AA | c uuc | AUG | GAG                        | ACA | UCU | No skipping        |
| 130    | H32A(+49+73)                         | CUU GU | A GAC | GCU | GCU                        | CAA | AAU | Skipping to 300 nM |

#### Antisense Oligonucleotides Directed at Exon 33

Antisense oligonucleotides directed at exon 33 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 14 shows differing efficiencies of two antisense 45 molecules directed at exon 33 acceptor splice site. H33A(+ 64+88) [SEQ ID NO:134] substantially induced exon 33 skipping when delivered into cells at a concentration of 10 nM. Table 28 below includes other antisense molecules tested at a concentration of 100, 200 and 300 nM. These 50 antisense molecules showed a variable ability to induce exon skipping.

#### TABLE 28

| SEQ ID | Antisense<br>oligonucleotide<br>name | Sequ     | ienc | e   |     |     |     |     |     | Ability to induce skipping |
|--------|--------------------------------------|----------|------|-----|-----|-----|-----|-----|-----|----------------------------|
| 131    | H33D(+09-11)                         | CAU      | GCA  | CAC | ACC | טטט | GCU | CC  |     | No skipping                |
| 132    | H33A(+53+76)                         | UCU      | GUA  | CAA | nca | GAC | GUC | CAG | nca | Skipping to 200 nM         |
| 133    | H33A(+30+56)                         | GUG      | טטט  | AUC | ACC | AUU | UCC | ACU | UCA | Skipping to 200 nM         |
| 134    | H33A(+64+88)                         | GCG<br>G | חכם  | GCU | טטט | ucu | GUA | CAA | ucu | Skipping to 10 nM          |

53

Antisense Oligonucleotides Directed at Exon 34

Antisense oligonucleotides directed at exon 34 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 29 below includes antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 29

| SEQ ID | Antisense<br>oligonucleotide<br>name | Sequence Ability to induce skipping                   |
|--------|--------------------------------------|---|
| 135    | H34A(+83+104)                        | UCC AUA UCU GUA GCU GGC No skipping                   |
| 136    | H34A(+143+165)                       | CCA GGC AAC UUC AGA AUC No skipping                   |
| 137    | H34A(-20+10)                         | UUU CUG UUA CCU GAA AAG Not tested<br>AAU UAU AAU GAA |
| 138    | H34A(+46+70)                         | CAU UCA UUU CCU UUC GCA Skipping to 300 nM            |
| 139    | H34A(+95+120)                        | UGA UCU CUU UGU CAA UUC Skipping to 300 CAU AUC UG nM |
| 140    | H34D(+10-20)                         | UUC AGU GAU AUA GGU UUU Not tested<br>ACC UUU CCC CAG |
| 41     | H34A(+72+96)                         | CUG UAG CUG CCA GCC AUU No skipping                   |

Antisense Oligonucleotides Directed at Exon 35

Antisense oligonucleotides directed at exon 35 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 15 shows differing efficiencies of antisense molecules directed at exon 35 acceptor splice site. H35A(+24+43) [SEQ ID NO:144] substantially induced exon 35 skipping when delivered into cells at a concentration of 20 nM. Table 30 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed no ability to induce exon skipping.

TABLE 30

| SEQ ID | Antisense<br>oligonucleotide<br>name | Seq | ienc | e   |     |     |     |     |    | ility to induce<br>ipping |
|--------|--------------------------------------|-----|------|-----|-----|-----|-----|-----|----|---------------------------|
| 142    | H35A(+141+161)                       | ucu | ucu  | GCU | CGG | GAG | GUG | ACA | Sk | ipping to 20 nM           |
| 143    | H35A(+116+135)                       | CCA | GUU  | ACU | AUU | CAG | AAG | AĊ  | No | skipping                  |
| 144    | H35A(+24+43)                         | UCU | UCA  | GGU | GCA | CCU | ucu | GU  | No | skipping                  |

Antisense Oligonucleotides Directed at Exon 36

Antisense oligonucleotides directed at exon 36 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

Antisense molecule H36A(+26+50) [SEQ ID NO:145] induced exon 36 skipping when delivered into cells at a concentration of 300 nM, as shown in FIG. 16.

Antisense Oligonucleotides Directed at Exon 37

Antisense oligonucleotides directed at exon 37 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 17 shows differing efficiencies of two antisense molecules directed at exon 37 acceptor splice site. H37A(+82+105) [SEQ ID NO:148] and H37A(+134+157) [SEQ ID NO:149] substantially induced exon 37 skipping when delivered into cells at a concentration of 10 nM. Table 31 below shows the antisense molecules tested.

Skipping to 10 nM

Skipping to 10 nM

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TABLE 31 Sequence Ability to induce skipping CGU GUA GAG UCC ACC UUU GGG CGU No skipping UAC UAA UUU CCU GCA GUG GUC ACC

Antisense Oligonucleotides Directed at Exon 38

55

Antisense oligonucleotide

H37A(+26+50)

H37A(+82+105)

H37A(+134+157)

name

SEQ ID

147

148

149

Antisense oligonucleotides directed at exon 38 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 18 illustrates antisense molecule H38A(+88+112) [SEQ ID NO:152], directed at exon 38 acceptor splice site. 20 H38A(+88+112) substantially induced exon 38 skipping when delivered into cells at a concentration of 10 nM. Table 32 below shows the antisense molecules tested and their ability to induce exon skipping.

Antisense Oligonucleotides Directed at Exon 40

56

Antisense oligonucleotides directed at exon 40 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 19 illustrates antisense molecule H40A(-05+17) [SEQ ID NO:157] directed at exon 40 acceptor splice site. H40A(-05+17) and H40A(+129+153) [SEQ ID NO:158] both substantially induced exon 40 skipping when delivered into cells at a concentration of 5 nM.

TABLE 32

UUC UGU GUG AAA UGG CUG CAA AUC

| SEQ ID | Antisense<br>oligonucleotide<br>name | Seq        | uenc | ė   |     |     |     |     | Ability to skipping | induce |
|--------|--------------------------------------|------------|------|-----|-----|-----|-----|-----|---------------------|--------|
| 150    | H38A(-01+19)                         | CCU        | UCA  | AAG | GAA | UGG | AGG | cc  | No skipping         |        |
| 151    | H38A(+59+83)                         | UGC        |      | AUU | UCA | GCC | ucc | AGU | Skipping to         | 10 nM  |
| 152    | H38A(+88+112)                        | UGA<br>UCA | 1022 | CUU | ccu | cuu | UCA | GAU | Skipping to         | 10 nM  |

Antisense Oligonucleotides Directed at Exon 39

Antisense oligonucleotides directed at exon 39 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described 45 above. above.

H39A(+62+85) [SEQ ID NO:153] induced exon 39 skipping when delivered into cells at a concentration of 100 nM. Table 33 below shows the antisense molecules tested and 50 their ability to induce exon skipping

Antisense Oligonucleotides Directed at Exon 42

Antisense oligonucleotides directed at exon 42 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

FIG. 20 illustrates antisense molecule H42A(-04+23) [SEQ ID NO:159], directed at exon 42 acceptor splice site. H42A(-4+23) and H42D(+19-02) [SEQ ID NO:161] both induced exon 42 skipping when delivered into cells at a concentration of 5 nM. Table 34 below shows the antisense molecules tested and their ability to induce exon 42 skip-

TABLE 33

| SEQ ID | Antisense<br>oligonucleotide<br>name | Seq | uenc | e   |     |     |     |     | Ability to induce skipping |
|--------|--------------------------------------|-----|------|-----|-----|-----|-----|-----|----------------------------|
| 153    | H39A(+62+85)                         | CUG | GCU  | UUC | ncn | CAU | CUG | UGA | Skipping to 100 nM         |
| 154    | H39A(+39+58)                         | GUU | GUA  | AGU | UGU | CUC | cuc | מט  | No skipping                |
| 155    | H39A(+102+121)                       | UUG | ucu  | GUA | ACA | GCU | GCU | GU  | No skipping                |
| 156    | H39D(+10-10)                         | GCU | CUA  | AUA | CCU | UGA | GAG | CA  | Skipping to 300 nM         |

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TABLE 34

| SEQ ID | Antisense<br>oligonucleotide<br>name | Sequence                               | Ability to induce            |
|--------|--------------------------------------|--|------------------------------|
| 159    | H42A(-4+23)                          | AUC GUU UCU UCA CGG ACA GUG<br>UGG UGC | skipping<br>Skipping to 5 nM |
| 160    | H42A(+86+109)                        | GGG CUU GUG AGA CAU GAG UGA            |                              |
| 161    | H42D(+19-02)                         | A CCU UCA GAG GAC UCC UCU<br>UGC       | Skipping to 5 nM             |

Antisense Oligonucleotides Directed at Exon 43

Antisense oligonucleotides directed at exon 43 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H43A(+101+120) [SEQ ID NO:163] induced exon 43 skipping when delivered into cells at a concentration of 25 nM. Table 35 below includes the antisense molecules tested and their ability to induce exon 43 skipping.

TABLE 35

| SEQ ID | Antisense<br>oligonucleotide<br>name | Sequence                             | Ability to induce skipping |
|--------|--------------------------------------|--------------------------------------|----------------------------|
| 162    | H43D(+10-15)                         | UAU GUG UUA CCU ACC CUU GUC<br>GGU C | Skipping to 100 nM         |
| 163    | H43A(+101+120)                       | GGA GAG AGC UUC CUG UAG CU           | Skipping to 25 nM          |
| 164    | H43A(+78+100)                        | UCA CCC UUU CCA CAG GCG UUG CA       | Skipping to 200 n M        |

Antisense Oligonucleotides Directed at Exon 44

Antisense oligonucleotides directed at exon 44 were prepared using similar methods as described above. Testing for 40 the ability of these antisense molecules to induce exon 44 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 165 to 167 in Table 1A.

Antisense Oligonucleotides Directed at Exon 45

Antisense oligonucleotides directed at exon 45 were prepared using similar methods as described above. Testing for the ability of these antisense molecules to induce exon 45 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 207 to 211 in Table 1A. Antisense Oligonucleotides Directed at Exon 46

Antisense oligonucleotides directed at exon 46 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 21 illustrates the efficiency of one antisense mol-45 ecule directed at exon 46 acceptor splice site. Antisense oligonucleotide H46A(+86+115) [SEQ ID NO:203] showed very strong ability to induce exon 46 skipping. Table 36 below includes antisense molecules tested. These antisense molecules showed varying ability to induce exon 46 skipping.

TABLE 36

| Antisense<br>oligonucleotide<br>name | Sequence  | Ability to induce skipping   |
|--------------------------------------|---|--|
| H46D(+16-04)                         | UUA CCU UGA CUU GCU CAA GC  | No skipping  |
| H46A(+90+109)                        | UCC AGG UUC AAG UGG GAU AC  | No skipping  |
| H46A(+86+115)                        | CUC UUU UCC AGG UUC AAG UGG GAU<br>ACU AGC                                | Good skipping<br>to 100 nM   |
| H46A(+107+137)                       | CAA GCU UUU CUU UUA GUU GCU GCU   | Good skipping<br>to 100 nM   |
|                                      | oligonucleotide<br>name<br>H46D(+16-04)<br>H46A(+90+109)<br>H46A(+86+115) | Oligonucleotide name  Sequence  H46D(+16-04)  UUA CCU UGA CUU GCU CAA GC  H46A(+90+109)  UCC AGG UUC AAG UGG GAU AC  H46A(+86+115)  CUC UUU UCC AGG UUC AAG UGG GAU ACU AGC  H46A(+107+137)  CAA GCU UUU CUU UUA GUU GCU GCU |

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| SEQ ID | Antisense<br>oligonucleótide<br>name | Sequence                        | Ability to induce |
|--------|--------------------------------------|---------------------------------|-------------------|
| 205    | H46A(+10+20)                         | UAU UCU UUU GUU CUU             | skipping          |
|        |                                      | AGA AAG                         | Weak skipping     |
| 206    | H46A(+50+77)                         | CUG CUU CCU CCA ACC AUA AAA CAA | Weak skipping     |

TABLE 36-cont

Antisense Oligonucleotides Directed at Exon 47

Antisense oligonucleotides directed at exon 47 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

H47A(+76+100) [SEQ ID NO:170] and H47A(-09+12) [SEQ ID NO:172] both induced exon 47 skipping when 20 human muscle cells using similar methods as described 25-02) [SEQ ID NO: 171] is yet to be prepared and tested.

Antisense Oligonucleotides Directed at Exon 50

Antisense oligonucleotides directed at exon 50 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

Antisense oligonucleotide molecule H50A(+02+30) 30 [SEQ ID NO: 173] was a strong inducer of exon skipping.

Further, H50A(+07+33) [SEQ ID NO:174] and H50D(+07-18) [SEQ ID NO:175] both induced exon 50 skipping when delivered into cells at a concentration of 100 nM.

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Antisense Oligonucleotides Directed at Exon 51

Antisense oligonucleotides directed at exon 51 were preabove.

FIG. 22 illustrates differing efficiencies of two antisense molecules directed at exon 51 acceptor splice site. Antisense oligonucleotide H51A(+66+90) [SEQ ID NO:180] showed 25 the stronger ability to induce exon 51 skipping. Table 37 below includes antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 51 skipping. The strongest inducers of exon skipping were antisense oligonucleotide H51A(+61+90) [SEQ ID NO: 179] and H51A(+66+95) [SEQ ID NO: 181].

TABLE 37

| SEQ ID | Antisense<br>oligonucleotide<br>name | Sequence  | Ability to induce skipping |
|--------|--------------------------------------|---|----------------------------|
| 176    | H51A(-01+25)                         | ACC AGA GUA ACA GUC<br>UGA GUA GGA GC                 | Faint skipping             |
| 177    | H51D(+16-07)                         | CUC AUA CCU UCU GCU<br>UGA UGA UC                     | Skipping at 300<br>nM      |
| 178    | H51A(+111+134)                       | UUC UGU CCA AGC CCG<br>GUU GAA AUC                    | Needs re-testing           |
| 179    | H51A(+61+90)                         | ACA UCA AGG AAG AUG<br>GCA UUU CUA GUU UGG            | Very strong<br>skipping    |
| 180    | H51A(+66+90)                         | ACA UCA AGG AAG AUG<br>GCA UUU CUA G                  | akipping                   |
| 191    | H51A(+66+95)                         | CUC CAA CAU CAA GGA<br>AGA UGG CAU UUC UAG            | Very strong<br>skipping    |
| 182    | H51D(+08-17)                         | AUC AUU UUU UCU CAU<br>ACC UUC UGC U                  | No skipping                |
| 183    | H51A/D(+08-17)<br>& (-15+?)          | AUC AUU UUU UCU CAU<br>ACC UUC UGC UAG GAG<br>CUA AAA | No skipping                |
| 184    | H51A(+175+195)                       | CAC CCA CCA UCA GCC<br>UCU GUG                        | No skipping                |
| 185    | H51A(+199+220)                       | AUC AUC UCG UUG AUA                                   | No skipping                |

61 Antisense Oligonucleotides Directed at Exon 52

Antisense oligonucleotides directed at exon 52 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described 5

FIG. 22 also shows differing efficiencies of four antisense molecules directed at exon 52 acceptor splice site. The most 62

effective antisense oligonucleotide for inducing exon 52 skipping was H52A(+17+37) [SEQ ID NO:188).

Table 38 below shows antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 50 skipping. Antisense molecules H52A(+12+41) [SEQ ID NO:187] and H52A(+17+37) [SEQ ID NO:188] showed the strongest exon 50 skipping at a concentration of 50 nM.

TABLE 38

| SEQ ID | Antisense<br>oligonucleotide<br>name | Sequence                                   | Ability to induce       |
|--------|--------------------------------------|--|-------------------------|
| 186    | H52A(-07+14)                         | UCC UGC AUU GUU GCC UGU AAG                | No skipping             |
| 187    | H52A(+12+41)                         | UCC AAC UGG GGA CGC CUC UGU UCC<br>AAA UCC | Very strong<br>skipping |
| 188    | H52A(+17+37)                         | ACU GGG GAC GCC UCU GUU CCA                | Skipping to             |
| 189    | H52A(+93+112)                        | CCG UAA UGA UUG UUC UAG CC                 | No skipping             |
| 190    | H52D (+05-15)                        | UGU UAA AAA ACU UAC UUC GA                 | No skipping             |

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Antisense Oligonucleotides Directed at Exon 53

Antisense oligonucleotides directed at exon 53 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

FIG. 22 also shows antisense molecule H53A(+39+69) [SEQ ID NO:193] directed at exon 53 acceptor splice site. This antisense oligonucleotide was able to induce exon 53 skipping at 5, 100, 300 and 600 nM. A "cocktail" of three exon 53 antisense oligonucleotides: H53A(+23+47) [SEQ ID NO:195], H53A(+150+176) [SEQ ID NO:196] and H53D(+14-07) [SEQ ID NO:194], was also tested, as shown in FIG. 20 and exhibited an ability to induce exon

Table 39 below includes other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 53 skipping. Antisense molecule H53A(+39+69) [SEQ ID NO:193] induced the strongest exon 53 skipping.

TABLE 39

| SEQ ID | Antisense<br>oligonucleotide<br>name | Seq     | uenc       | e        |          |          |     | Ability to induce skipping      |
|--------|--------------------------------------|---------|------------|----------|----------|----------|-----|---------------------------------|
| 191    | H53A (+45+69)                        | CAU     |            | ACU<br>G | GUU      | GCC      | UCC | Faint skipping at<br>50 nM      |
| 192    | H53A(+39+62)                         |         | UUG<br>GUG | ccu      | ccg      | GUU      | CUG | Faint skipping at<br>50 nM      |
| 193    | H53A(+39+69)                         | CAU     |            |          | GUU      | GCC<br>G | UCC | Strong skipping<br>to 50 nM     |
| 194    | H53D(+14-07)                         | UAC     | UAA        | ccu      | UGG      | מממ      | CUG | Very faint<br>skipping to 50 nM |
| 195    | H53A(+23+47)                         | 100,000 | AAG<br>UUC | C40-34   | ouc<br>c | UUG      |     | Very faint<br>skipping to 50 nM |
| 196    | H53A(+150+176)                       |         | AUA<br>UGA |          | ACC      | CUC      | cuu | Very faint<br>skipping to 50 nM |
| 97     | H53D(+20-05)                         | CUA     | ACC        | 244      | GUU      | UCU      | GUG | Not made yet                    |
|        |                                      |         |            |          |          |          |     |                                 |

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TABLE 39-continued

| SEQ ID | Antisense<br>oligonucleotide<br>name | Sequence                               | Ability to induce skipping |
|--------|--------------------------------------|--|----------------------------|
| 198    | H53D(+09-18)                         | GGU AUC UUU GAU ACU<br>AAC CUU GGU UUC | Faint at 600 nM            |
| 199    | H53A(-12+10)                         | AUU CUU UCA ACU AGA<br>AUA AAA G       | No skipping                |
| 200    | H53A(-07+18)                         | GAU UCU GAA UUG UUU<br>CAA CUA GAA U   | No skipping                |
| 201    | H53A(+07+26)                         | AUC CCA CUG AUU CUG AAU<br>UC          | No skipping                |
| 202    | H53A(+124+145)                       | UUG GCU CUG GCC UGU CCU                | No skipping                |

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86
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Human 2'-O-methyl phosphorothicate antisense

<212 > TYPE: RNA

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210 SEQ ID NO 157

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130 -continued <220> FEATURE: <220> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense 400> SEQUENCE: 185 aucaucucgu ugauauccuc aa 22 <210> SEQ ID NO 186 (211 > LENGTH: 21 <212 > TYPE: RNA 213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 186 uccugcauug uugccuguaa g 21 <210> SEQ ID NO 187 <211 > LENGTH: 30 <212 TYPE: RNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 187 uccaacuggg gacgccucug uuccaaauce 30 <210> SEQ ID NO 188 211 > LENGTH: 21 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 188 21 acuggggacg ccucuguucc a \*210 > SEQ ID NO 189 <211 > LENGTH: 20 <212> TYPE: RNA 1213> ORGANISM: Artificial Sequence (220 > PEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothicate antisense oligonucleotide 400> SEQUENCE: 189 20 ceguaaugau uguucuagee \$210 > SEQ ID NO 190 \*211 > LENGTH: 20 <212 » TYPE: RNA (213) ORGANISM; Artificial Sequence \*223 OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothioate antisense oligonucleotide <400> SEQUENCE: 190 20 uguuaaaaaa cuuacuucga

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<220> FEATURE:

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21

25

<210> SEQ ID NO 195 «211» LENGTH: 25

\*212 > TYPE: RNA

\*213 ORGANISM: Artificial Sequence

\*220> FEATURE:

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\*210 > SEQ 1D NO 196

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What is claimed is:

1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the base sequence com-prises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and

2. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 20 to 31 bases comprising a base

sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping, or a pharwherein the antisense oligonucleotide induces exon 53 skip25 maceutically acceptable salt thereof; and (ii) a pharmaceutically acceptable carrier.

SRPT-VYDS-0002869

# EXHIBIT 3

US010266827B2

# (12) United States Patent Wilton et al.

(10) Patent No.: US 10,266,827 B2

(45) Date of Patent:

\*Apr. 23, 2019

### (54) ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

- (71) Applicant: The University of Western Australia, Crawley (AU)
- (72) Inventors: Stephen Donald Wilton, Applecross (AU); Sue Fletcher, Bayswater (AU); Graham McClorey, Bayswater (AU)
- (73) Assignee: The University of Western Australia, Crawley (AU)
- (\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

- (21) Appl. No.: 16/112,453
- (22) Filed: Aug. 24, 2018
- (65) Prior Publication Data

US 2019/0062742 A1 Feb. 28, 2019

## Related U.S. Application Data

(63) Continuation of application No. 15/274,772, filed on Sep. 23, 2016, now abandoned, which is a continuation of application No. 14/740,097, filed on Jun. 15, 2015, now Pat. No. 9,605,262, which is a continuation of application No. 13/741,150, filed on Jan. 14, 2013, now abandoned, which is a continuation of application No. 13/168,857, filed on Jun. 24, 2011, now abandoned, which is a continuation of application No. 12/837,359, filed on Jul. 15, 2010, now Pat. No. 8,232,384, which is a continuation of application No. 11/570,691, filed as application No. PCT/AU2005/000943 on Jun. 28, 2005, now Pat. No. 7,807,816.

# (30) Foreign Application Priority Data

Jun. 28, 2004 (AU) ...... 2004903474

(51) Int. Cl. C07H 21/04 (2006.01) C12N 15/113 (2010.01)

(52) U.S. Cl.

CPC ....... C12N 15/113 (2013.01); C12N 2310/11 (2013.01); C12N 2310/315 (2013.01); C12N 2310/321 (2013.01); C12N 2310/3233 (2013.01); C12N 2310/33 (2013.01); C12N 2310/3341 (2013.01); C12N 2310/3519 (2013.01); C12N 2320/30 (2013.01); C12N 2320/33 (2013.01)

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Primary Examiner — Kimberly Chong (74) Attorney, Agent, or Firm — Sterne, Kessler, Goldstein & Fox P.L.L.C.

### (57) ABSTRACT

An antisense molecule capable of binding to a selected target site to induce exon skipping in the dystrophin gene, as set forth in SEQ ID NO: 1 to 214.

### 2 Claims, 22 Drawing Sheets

Specification includes a Sequence Listing.

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ucaugcacugagugaccucuuucucgcagGCGCUAGCUGGAGCA/////CCGUGCAGACUGACGgucucau ESE

**SEQ ID NO:213** 

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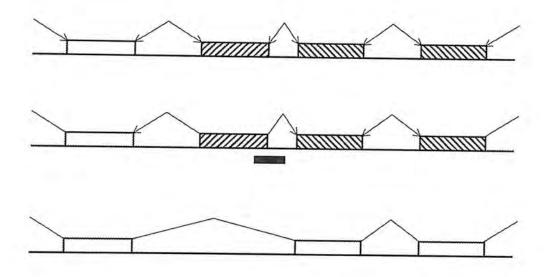


FIGURE 2

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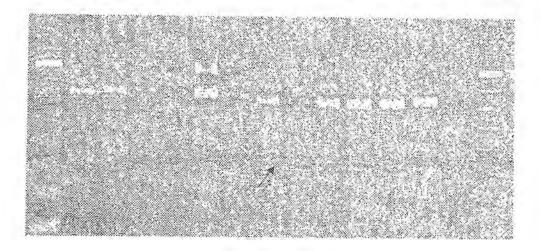


FIGURE 3

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H7A(+45+67) H7A(+2+26)
M 600 300 100 50 20 600NM 600 300 100 50 20 600N M

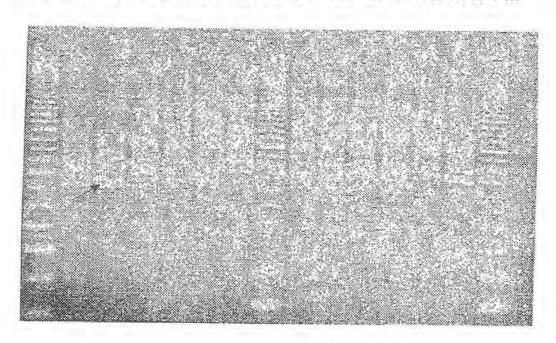


FIGURE 4

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H6D(+4-21) H6D(+18+4)

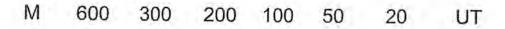
(nM)

M 600 300 100 50 20 600N M 600 300 100 50 20 UT

FIGURE 5

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6A(+69+91)



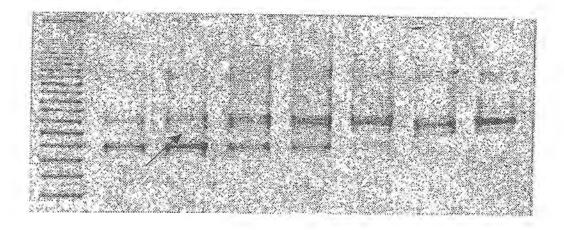


FIGURE 6

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H4A(+13+32)

M 600 300 100 50 20 UT Neg M

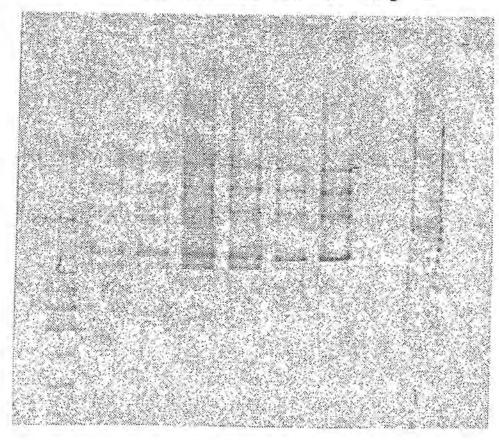


FIGURE 7

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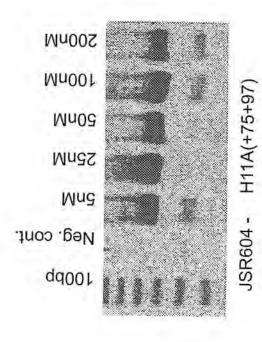
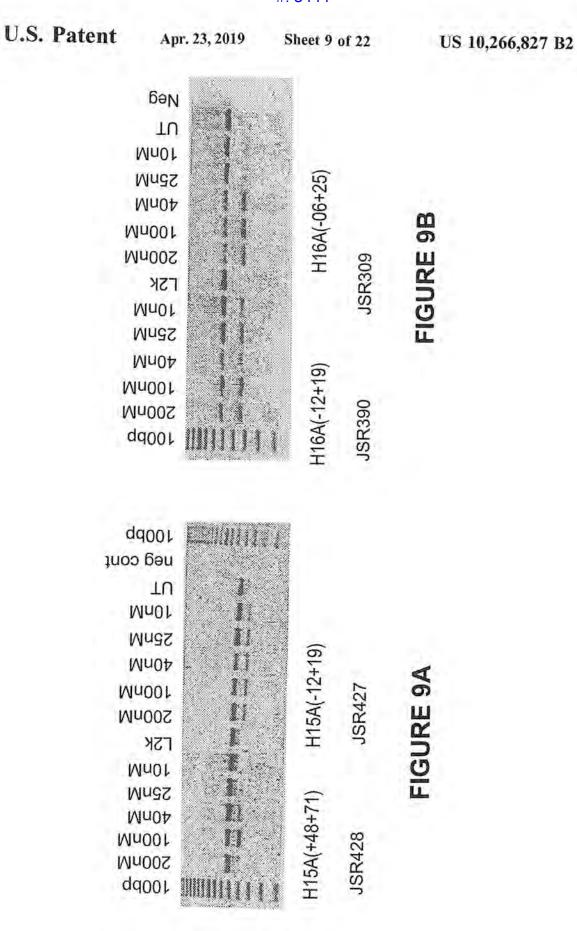


FIGURE 8B

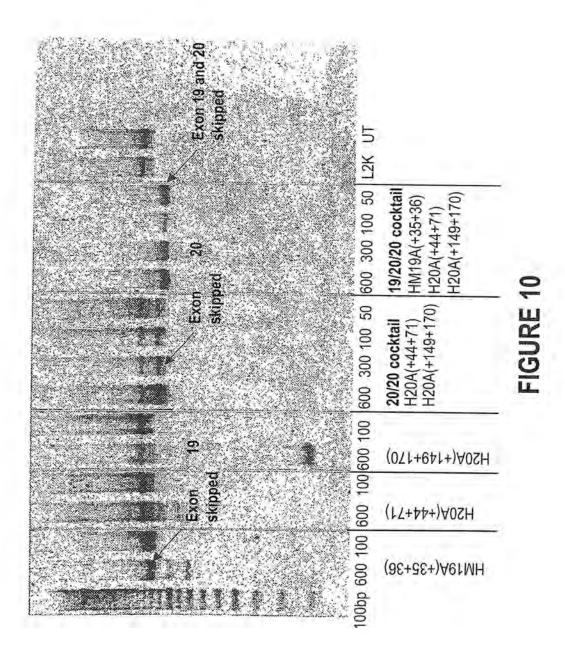
100bp Mn002 H12A(+52+75) Mn001 Mn02 MndS JSR610 -Mug



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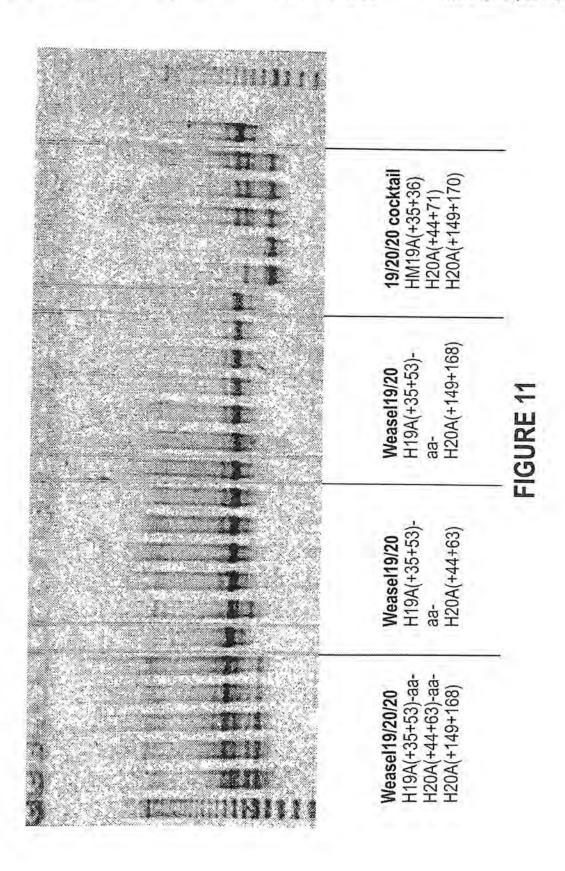
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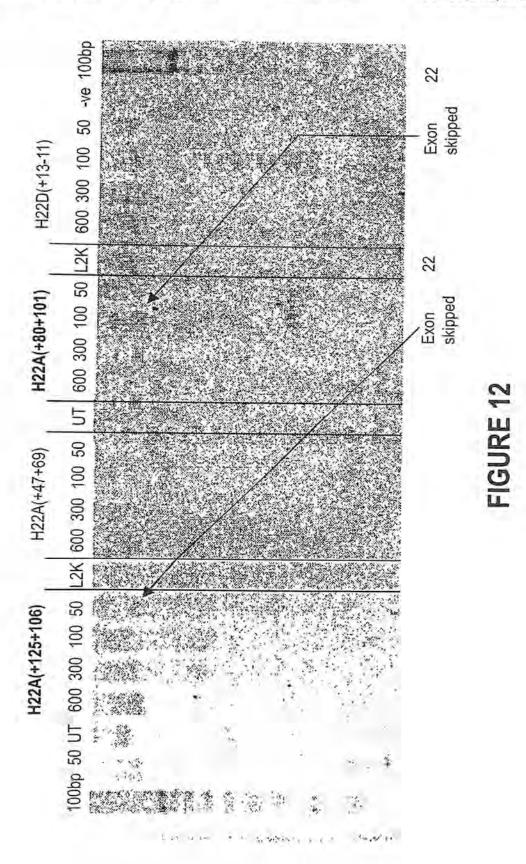
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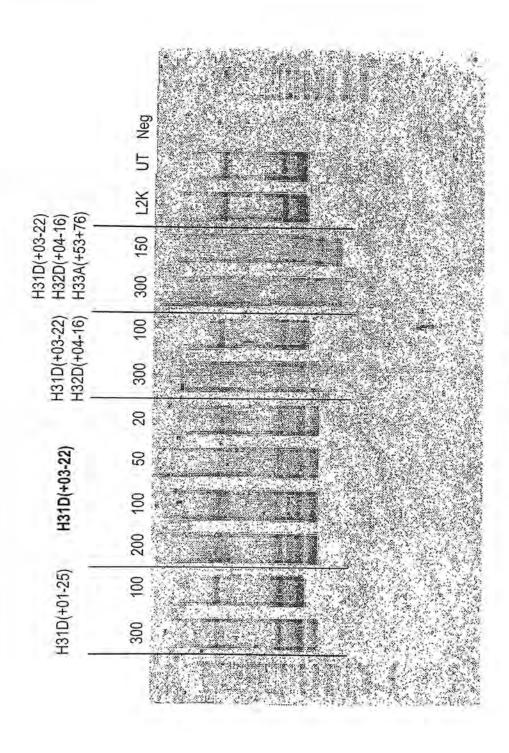
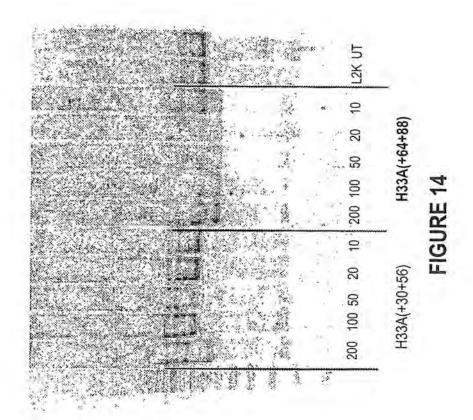


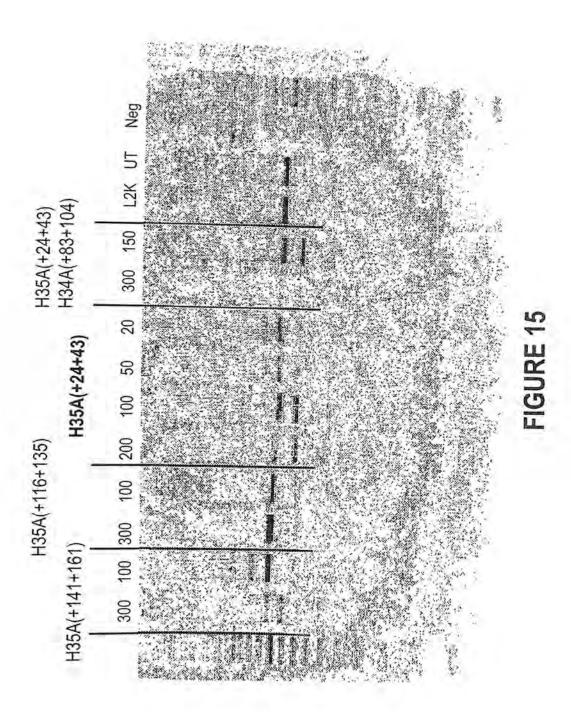
FIGURE 13

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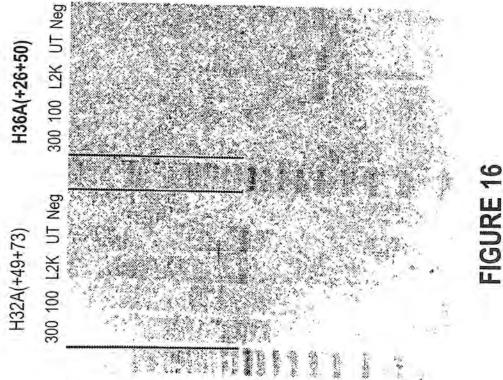


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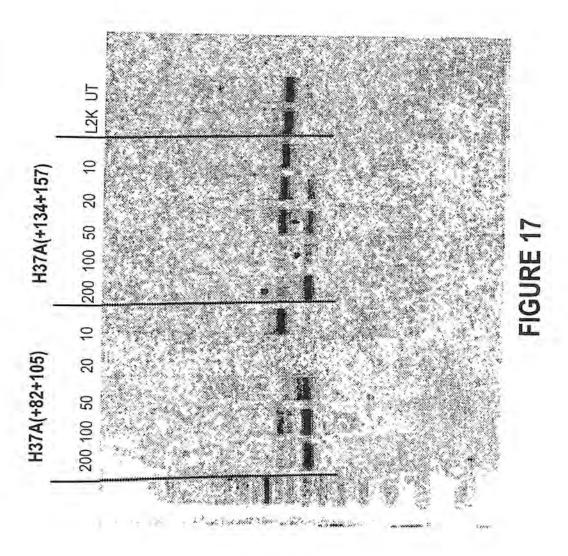
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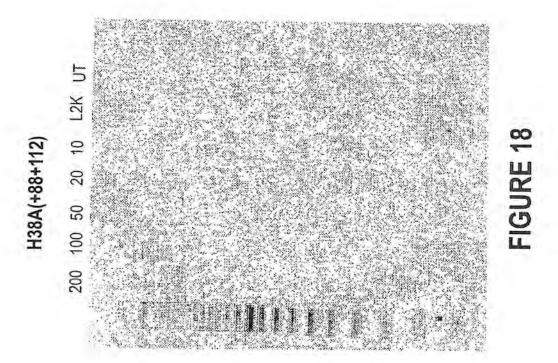
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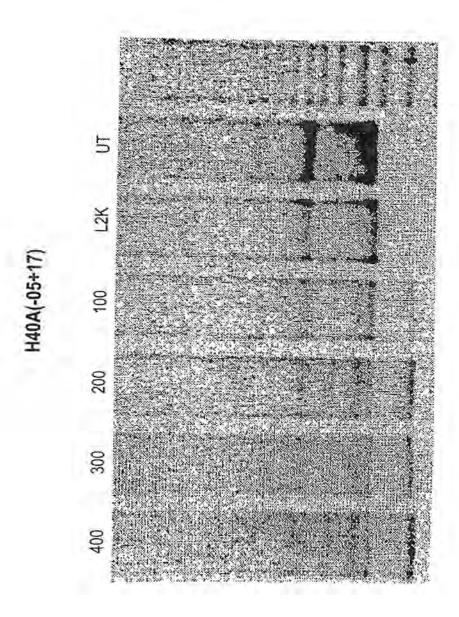


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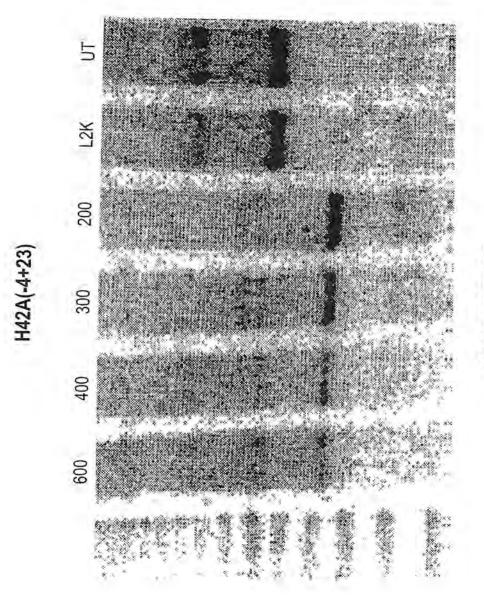
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## H46A(+86+115)

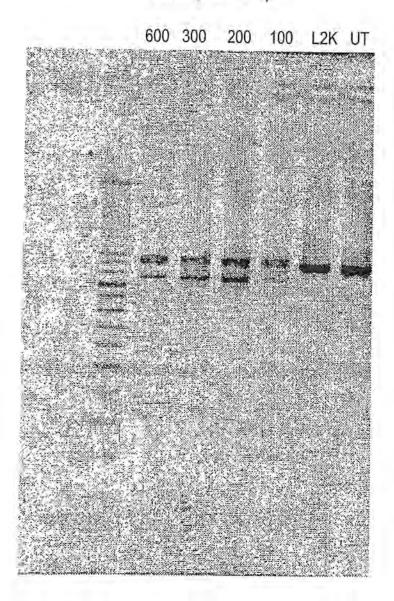
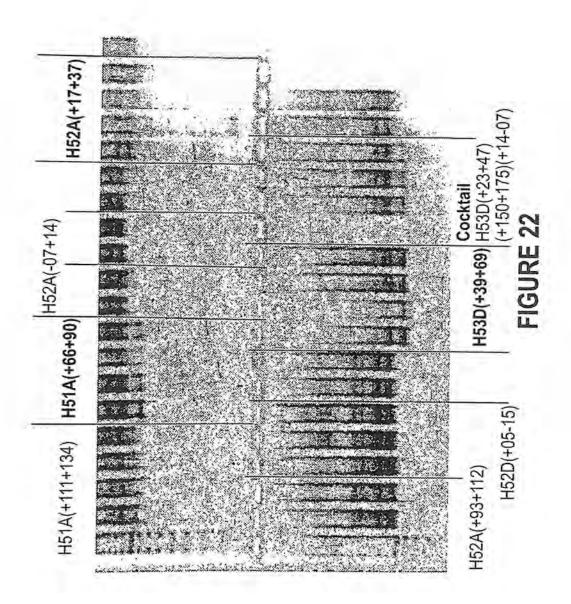


FIGURE 21

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### ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

# CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 15/274,772, filed Sep. 23, 2016, now pending, which application is a continuation of U.S. patent application Ser. No. 14/740,097, filed Jun. 15, 2015, now issued as U.S. Pat. No. 9,605,262, which application is a continuation of U.S. patent application Ser. No. 13/741,150, filed Jan. 14, 2013, now abandoned, which application is a continuation of U.S. patent application Ser. No. 13/168,857, filed Jun. 24, 2011, now abandoned, which application is a continuation of U.S. patent application Ser. No. 12/837,359, filed Jul. 15, 2010, now issued as U.S. Pat. No. 8,232,384, which application is a continuation of U.S. patent application Ser. No. 11/570,691, filed Jan. 15, 2008, now issued as U.S. Pat. No. 7.807,816, which application is a 35 U.S.C. § 371 National Phase Application of PCT/AU2005/000943, filed Jun. 28, 2005, which claims priority to Australian Patent Application No. 2004903474, filed Jun. 28, 2004; which applications are each incorporated herein by reference in their entireties.

## STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

This invention was made with government support under <sup>30</sup> grant number R01 NS044146 awarded by the National Institutes of Health. The government has certain rights in the invention.

#### STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with the application is provided in text format in liew of a paper copy, and is hereby incorporated by reference into the specification. The name of 40 the text file containing the Sequence Listing is 4140.01500B1\_SL.txt. The text file is 62,078 bytes, was created on Aug. 23, 2018 and is being submitted electronically via EFS-Web.

#### FIELD OF THE INVENTION

The present invention relates to novel antisense compounds and compositions suitable for facilitating exon skipping. It also provides methods for inducing exon skipping 50 using the novel antisense compounds as well as therapeutic compositions adapted for use in the methods of the invention.

#### BACKGROUND ART

Significant effort is currently being expended researching methods for suppressing or compensating for disease-causing mutations in genes. Antisense technologies are being developed using a range of chemistries to affect gene expression at a variety of different levels (transcription, splicing, stability, translation). Much of that research has focused on the use of antisense compounds to correct or compensate for abnormal or disease-associated genes in a myriad of different conditions.

Antisense molecules are able to inhibit gene expression with exquisite specificity and because of this many research

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efforts concerning oligonucleotides as modulators of gene expression have focused on inhibiting the expression of targeted genes such as oncogenes or viral genes. The antisense oligonucleotides are directed either against RNA (sense strand) or against DNA where they form triplex structures inhibiting transcription by RNA polymerase II. To achieve a desired effect in specific gene down-regulation, the oligonucleotides must either promote the decay of the targeted mRNA or block translation of that mRNA, thereby effectively preventing de novo synthesis of the undesirable target protein.

Such techniques are not useful where the object is to up-regulate production of the native protein or compensate for mutations which induce premature termination of translation such as nonsense or frame-shifting mutations. Furthermore, in cases where a normally functional protein is prematurely terminated because of mutations therein, a means for restoring some functional protein production through antisense technology has been shown to be possible through intervention during the splicing processes (Sierakowska H, et al., (1996) Proc Natl Acad Sci USA 93, 12840-12844; Wilton S D, et al., (1999) Neuromusc Disorders 9, 330-338; van Deutekom J C et al., (2001) Human Mol Genet 10, 1547-1554). In these cases, the defective gene transcript should not be subjected to targeted degradation so the antisense oligonucleotide chemistry should not promote target mRNA decay.

In a variety of genetic diseases, the effects of mutations on the eventual expression of a gene can be modulated through a process of targeted exon skipping during the splicing process. The splicing process is directed by complex multiparticle machinery that brings adjacent exon-intron junctions in pre-mRNA into close proximity and performs cleavage of phosphodiester bonds at the ends of the introns with their subsequent reformation between exons that are to be spliced together. This complex and highly precise process is mediated by sequence motifs in the pre-mRNA that are relatively short semi-conserved RNA segments to which bind the various nuclear splicing factors that are then involved in the splicing reactions. By changing the way the splicing machinery reads or recognises the motifs involved in pre-mRNA processing, it is possible to create differentially spliced mRNA molecules. It has now been recognised that the majority of human genes are alternatively spliced during normal gene expression, although the mechanisms invoked have not been identified. Using antisense oligonucleotides, it has been shown that errors and deficiencies in a coded mRNA could be bypassed or removed from the mature gene transcripts.

In nature, the extent of genetic deletion or exon skipping in the splicing process is not fully understood, although many instances have been documented to occur, generally at very low levels (Sherrat T G, et al., (1993) Am J Hum Genet 53, 1007-1015). However, it is recognised that if exons associated with disease-causing mutations can be specifically deleted from some genes, a shortened protein product can sometimes be produced that has similar biological properties of the native protein or has sufficient biological activity to ameliorate the disease caused by mutations associated with the target exon (Lu Q L, et al., (2003) Nature Medicine 9, 1009-1014; Aartsma-Rus A et al., (2004) Am J Hum Genet 74: 83-92).

This process of targeted exon skipping is likely to be particularly useful in long genes where there are many exons and introns, where there is redundancy in the genetic constitution of the exons or where a protein is able to function without one or more particular exons (e.g. with the dystro-

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phin gene, which consists of 79 exons; or possibly some collagen genes which encode for repeated blocks of sequence or the huge nebulin or titin genes which are comprised of ~80 and over 370 exons, respectively).

Efforts to redirect gene processing for the treatment of genetic diseases associated with truncations caused by mutations in various genes have focused on the use of antisense oligonucleotides that either: (1) fully or partially overlap with the elements involved in the splicing process; or (2) bind to the pre-mRNA at a position sufficiently close to the element to disrupt the binding and function of the splicing factors that would normally mediate a particular splicing reaction which occurs at that element (e.g., binds to the pre-mRNA at a position within 3, 6, or 9 nucleotides of the element to be blocked).

For example, modulation of mutant dystrophin premRNA splicing with antisense oligoribonucleotides has been reported both in vitro and in vivo. In one type of dystrophin mutation reported in Japan, a 52-base pair deletion mutation causes exon 19 to be removed with the 20 flanking introns during the splicing process (Matsuo et al., (1991) *J Clin Invest.*, 87:2127-2131). An in vitro minigene splicing system has been used to show that a 31-mer 2'-O-methyl oligoribonucleotide complementary to the 5' half of the deleted sequence in dystrophin Kobe exon 19 2s inhibited splicing of wild-type pre-mRNA (Takeshima et al. (1995), *J. Clin. Invest.*, 95, 515-520). The same oligonucleotide was used to induce exon skipping from the native dystrophin gene transcript in human cultured lymphoblastoid cells.

Dunckley et al., (1997) Nucleosides & Nucleotides, 16, 1665-1668 described in vitro constructs for analysis of splicing around exon 23 of mutated dystrophin in the mdx mouse mutant, a model for muscular dystrophy. Plans to analyse these constructs in vitro using 2' modified oligonucleotides targeted to splice sites within and adjacent to mouse dystrophin exon 23 were discussed, though no target sites or sequences were given.

2'-O-methyl oligoribonucleotides were subsequently reported to correct dystrophin deficiency in myoblasts from 40 the mdx mouse from this group. An antisense oligonucleotide targeted to the 3' splice site of murine dystrophin intron 22 was reported to cause skipping of the mutant exon as well as several flanking exons and created a novel in-frame dystrophin transcript with a novel internal deletion. This 4s mutated dystrophin was expressed in 1-2% of antisense treated mdx myotubes. Use of other oligonucleotide modifications such as 2'-O-methoxyethyl phosphodiesters are described (Dunckley et al. (1998) Human Mol. Genetics, 5, 1083-90).

Thus, antisense molecules may provide a tool in the treatment of genetic disorders such as Duchenne Muscular Dystrophy (DMD). However, attempts to induce exon skipping using antisense molecules have had mixed success. Studies on dystrophin exon 19, where successful skipping of that exon from the dystrophin pre-mRNA was achieved using a variety of antisense molecules directed at the flanking splice sites or motifs within the exon involved in exon definition as described by Errington et al. (2003) *J Gen Med* 5, 518-527".

In contrast to the apparent ease of exon 19 skipping, the first report of exon 23 skipping in the mdx mouse by Dunckley et al., (1998) is now considered to be reporting only a naturally occurring revertant transcript or artefact rather than any true antisense activity. In addition to not consistently generating transcripts missing exon 23, Dunckley et al., (1998) did not show any time course of induced

exon skipping, or even titration of antisense oligonucleotides, to demonstrate dose dependent effects where the levels of exon skipping corresponded with increasing or decreasing amounts of antisense oligonucleotide. Furthermore, this work could not be replicated by other researchers.

The first example of specific and reproducible exon skipping in the mdx mouse model was reported by Wilton et al., (1999) Neuromuscular Disorders 9, 330-338. By directing an antisense molecule to the donor splice site, consistent and efficient exon 23 skipping was induced in the dystrophin mRNA within 6 hours of treatment of the cultured cells. Wilton et al., (1999), also describe targeting the acceptor region of the mouse dystrophin pre-mRNA with longer antisense oligonucleotides and being unable to repeat the published results of Dunckley et al., (1998). No exon skipping, either 23 alone or multiple removal of several flanking exons, could be reproducibly detected using a selection of antiseuse oligonucleotides directed at the acceptor splice site of intron 22.

While the first antisense oligonucleotide directed at the intron 23 donor splice site induced consistent exon skipping in primary cultured myoblasts, this compound was found to be much less efficient in immortalized cell cultures expressing higher levels of dystrophin. However, with refined targeting and antisense oligonucleotide design, the efficiency of specific exon removal was increased by almost an order of magnitude (see Mann C J et al., (2002) J Gen Med 4, 644-654).

Thus, there remains a need to provide antisense oligonucleotides capable of binding to and modifying the splicing of a target nucleotide sequence. Simply directing the antisense oligonucleotides to motifs presumed to be crucial for splicing is no guarantee of the efficacy of that compound in a therapeutic setting.

#### SUMMARY OF THE INVENTION

The present invention provides antisense molecule compounds and compositions suitable for binding to RNA motifs involved in the splicing of pre-mRNA that are able to induce specific and efficient exon skipping and a method for their use thereof.

The choice of target selection plays a crucial role in the efficiency of exon skipping and hence its subsequent application of a potential therapy. Simply designing antisense molecules to target regions of pre-mRNA presumed to be involved in splicing is no guarantee of inducing efficient and specific exon skipping. The most obvious or readily defined targets for splicing intervention are the donor and acceptor splice sites although there are less defined or conserved motifs including exonic splicing enhancers, silencing elements and branch points.

The acceptor and donor splice sites have consensus sequences of about 16 and 8 bases respectively (see FIG. 1 for schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process).

According to a first aspect, the invention provides antisense molecules capable of binding to a selected target to induce exon skipping.

For example, to induce exon skipping in exons 3 to 8, 10 to 16, 19 to 40, 42 to 44, 46, 47, and 50 to 53 in the Dystrophin gene transcript the antisense molecules are preferably selected from the group listed in Table 1A.

In a further example, it is possible to combine two or more antisense oligonucleotides of the present invention together to induce multiple exon skipping in exons 19-20, and 53.

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This is a similar concept to targeting of a single exon. A combination or "cocktail" of antisense oligonucleotides are directed at adjacent exons to induce efficient exon skipping.

In another example, to induce emotion exon skipping. 19-20, 31, 34 and 53 it is possible to improve exon skipping of a single exon by joining together two or more antisense oligonucleotide molecules. This concept is termed by the inventor as a "weasel", an example of a cunningly designed antisense oligonucleotide. A similar concept has been described in Aartsma-Rus A et al., (2004) Am J Hum Genet 1074: 83-92).

According to a second aspect, the present invention provides antisense molecules selected and or adapted to aid in the prophylactic or therapeutic treatment of a genetic disorder comprising at least an antisense molecule in a form 15 suitable for delivery to a patient.

According to a third aspect, the invention provides a method for treating a patient suffering from a genetic disease wherein there is a mutation in a gene encoding a particular protein and the affect of the mutation can be abrogated by 20 exon skipping, comprising the steps of: (a) selecting an antisense molecule in accordance with the methods described herein; and (b) administering the molecule to a patient in need of such treatment.

The invention also addresses the use of purified and 25 isolated antisense oligonucleotides of the invention, for the manufacture of a medicament for treatment of a genetic disease.

The invention further provides a method of treating a condition characterised by Duchenne muscular dystrophy, 30 which method comprises administering to a patient in need of treatment an effective amount of an appropriately designed antisense oligonucleotide of the invention, relevant to the particular genetic lesion in that patient. Further, the invention provides a method for prophylactically treating a 35 patient to prevent or at least minimise Duchene muscular dystrophy, comprising the step of administering to the patient an effective amount of an antisense oligonucleotide or a pharmaceutical composition comprising one or more of these biological molecules.

The invention also provides kits for treating a genetic disease, which kits comprise at least a antisense oligonucleotide of the present invention, packaged in a suitable container and instructions for its use.

Other aspects and advantages of the invention will 45 become apparent to those skilled in the art from a review of the ensuing description, which proceeds with reference to the following figures.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 Schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process (SEQ ID NOS: 213 and 214).

FIG. 2. Diagrammatic representation of the concept of antisense oligonucleotide induced exon skipping to by-pass disease-causing mutations (not drawn to scale). The hatched box represents an exon carrying a mutation that prevents the translation of the rest of the mRNA into a protein. The solid black bar represents an antisense oligonucleotide that prevents inclusion of that exon in the mature mRNA.

FIG. 3 Gel electrophoresis showing differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. The preferred compound [FI8A(-06+18)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured normal human muscle cells. The less preferred antisense oligonucleotide

[H8A(-06+14)] also induces efficient exon skipping, but at much higher concentrations. Other antisense oligonucleotides directed at exon 8 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

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FIG. 4 Gel electrophoresis showing differing efficiencies of two antisense molecules directed at internal domains within exon 7, presumably exon splicing enhancers. The preferred compound [H7A(+45+67)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells. The less preferred antisense oligonucleotide [H7A(+2+26)] induces only low levels of exon skipping at the higher transfection concentrations. Other antisense oligonucleotides directed at exon 7 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

FIG. 5 Gel electrophoresis showing an example of low efficiency exon 6 skipping using two non-preferred antisense molecules directed at human exon 6 donor splice site. Levels of induced exon 6 skipping are either very low [H6D(+04-21)] or almost undetectable [H6D(+18-04)]. These are examples of non-preferred antisense oligonucleotides to demonstrate that antisense oligonucleotide design plays a crucial role in the efficacy of these compounds.

FIG. 6 Gel electrophoresis showing strong and efficient human exon 6 skipping using an antisense molecules [H6A (+69+91)] directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells.

FIG. 7 Gel electrophoresis showing strong human exon 4 skipping using an antisense molecule H4A(+13+32) directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells,

FIG. 8A Gel electrophoresis showing strong human exon 12 skipping using antisense molecule H12A(+52+75) directed at exon 12 internal domain.

 FIG. 8B Gel electrophoresis showing strong human exon
 11 skipping using antisense molecule H11A(+75+97) directed at an exon 11 internal domain.

FIG. 9A Gel electrophoresis showing strong human exon 15 skipping using antisense molecules H15A(+48+71) and H15A(-12+19) directed at an exon 15 internal domain.

FIG. 9B Gel electrophoresis showing strong human exon 16 skipping using antisense molecules H16A(-12+19) and H16A(-06+25).

FIG. 10 Gel electrophoresis showing human exon 19/20 skipping using antisense molecules H20A(+44+71) and
H20A(+149+170) directed at an exon 20 and a "cocktail" of antisense oligonucleotides H19A(+35+65, H20A(+44+71) and H20A(+149+170) directed at exons 19/20.

FIG. 11 Gel electrophoresis showing human exon 19/20 skipping using "weasels" directed at exons 19 and 20.

FIG. 12 Gel electrophoresis showing exon 22 skipping using antisense molecules H22A(+125+106), H22A(+47+69), H22A(+80+101) and H22D(+13-11) directed at exon 22.

FIG. 13 Gel electrophoresis showing exon 31 skipping using antisense molecules H31D(+01-25) and H31D(+03-22); and a "cocktail" of antisense molecules directed at exon 31.

FIG. 14 Gel electrophoresis showing exon 33 skipping using antisense molecules H33A(+30+56) and H33A(+64+88) directed at exon 33.

FIG. 15 Gel electrophoresis showing exon 35 skipping using antisense molecules H35A(+141+161), H35A(+116+

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135), and H35A(+24+43) and a "cocktail of two antisense molecules, directed at exon 35.

FIG. 16 Gel electrophoresis showing exon 36 skipping using antisense molecules H32A(+49+73) and H36A(+26+50) directed at exon 36.

FIG. 17 Gel electrophoresis showing exon 37 skipping using antisense molecules H37A(+82+105) and H37A(+134+157) directed at exon 37.

FIG. 18 Gel electrophoresis showing exon 38 skipping using antisense molecule H38A(+88+112) directed at exon 10 38.

FIG. 19 Gel electrophoresis showing exon 40 skipping using antisense molecule H40A(-05+17) directed at exon 40.

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FIG. 20 Gel electrophoresis showing exon 42 skipping using antisense molecule H42A(-04+23) directed at exon 42.

FIG. 21 Gel electrophoresis showing exon 46 skipping using antisense molecule H46A(+86+115) directed a# exon 46

FIG. 22 Gel electrophoresis showing exon 51, exon 52 and exon 53 skipping using various antisense molecules directed at exons 51, 52 and 53, respectively. A "cocktail" of antisense molecules is also shown directed at exon 53,

## BRIEF DESCRIPTION OF THE SEQUENCE LISTINGS

#### TABLE 1A

Description of 2°-0-methyl phosphorothicate antisense oligonuclectides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2°-0-methyl antisense oligonuclectides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| EQ | ID SEQUENCE  | NU         | CLEO     | FIDE  | SEQU | JENCI | (5  | -3') |     |     |
|----|--------------|------------|----------|-------|------|-------|-----|------|-----|-----|
| 1  | H8A(-06+18)  | GAI        | J AGO    | g UGC | UAU  | CA    | CAU | cuc  | UAA |     |
| 2  | H8A(-03+18)  | GA         | J AGO    | ugo   | UAU  | CAZ   | CAU | cug  |     |     |
| 3  | H8A (-07+1B) | GAU        | AGO      | UGC   | UAL  | CAF   | CAU | CUG  | UAA | G   |
| 4  | H8A(-06+14)  | GGU        | J GGU    | AUC   | AAC  | AUC   | UGU | AA   |     |     |
| 5  | H8A (-10+10) | GUA        | UCA      | ACA   | UCU  | GUA   | AGC | AC   |     |     |
| 6  | H7A (+45+67) | UGC        | AUG      | טטט   | CAG  | UCG   | DUG | UGU  | GG  |     |
| 7  | H7A (+02+26) | CAC        | UAU      | UCC   | AGU  | CAA   | AUA | GGU  | COG | G   |
| 8  | H7D (+15-10) | AUU        | UAC      | CAA   | ccu  | UCA   | GGA | UCG  | AGU | A   |
| 9  | H7A (-18+03) | GGC        | CUA      | AAA   | CAC  | AUA   | CAC | AUA  |     |     |
| 10 | C6A (-10+10) | CAU        | טטט      | UGA   | ccu  | ACA   | UGU | GG   |     |     |
| 11 | C6A(-14+06)  | טטט        | GAC      | CUA   | CAU  | GUG   | GAA | AG   |     |     |
| 12 | C6A (-14+12) | UAC        | AUU      | טטט   | GAC  | CUA   | CAU | GUG  | GAA | AG  |
| 13 | C6A(-13+09)  | AUU        | טטט      | GAC   | CUA  | CAU   | GGG | AAA  | G   |     |
| 14 | CH6A(+69+91) | UAC        | GAG      | UUG   | AUU  | GUC   | GGA | ccc  | AG  |     |
| 15 | C6D (+12-13) | GUG        | GUC      | UCC   | UUA  | ccu   | AUG | ACU  | GUG | G   |
| 16 | C6D (+06-11) | GGU        | cuc      | caa   | ACC  | UAU   | GA  |      |     |     |
| 17 | H6D (+04-21) | UGU        | cuc      | AGU   | AAU  | cuu   | cuu | ACC  | UAU |     |
| 18 | H6D (+18-04) | ucu        | UAC      | CUA   | UGA  | CUA   | UGG | AUG  | AGA |     |
| 19 | H4A(+13+32)  | GCA        | UGA      | ACU   | CUU  | GUG   | GAU | CC   |     |     |
| 20 | H4D(+04-16)  | CCA        | GGG      | UAC   | UAC  | UUA   | CAU | UA   |     |     |
| 21 | H4D (-24-44) | AUC        | GUG      | ugu   | CAC  | AGC   | AUC | CAG  |     |     |
| 22 | H4A(+11+40)  | COO        | UCA      | GGG   | CAU  | GAA   | cuc | UUG  | UGG | AUG |
| 23 | H3A(+30+60)  | UAG<br>ACU |          | GCG   | ccu  | CCC   | AUC | CUG  | UAG | GU  |
| 24 | H3A(+35+65)  | AGG<br>AGG | UCU<br>U | AGG   | AGG  | CGC   | cuc | CCA  | ncc | UGU |

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### TABLE 1A-continued

Description of 2'-0-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-0-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ | ID SEQUENCE          | NUCLEOTIDE SEQUENCE (5'-3')                  |
|-----|----------------------|--|
| 2   | 5 H3A(+30+54)        | GCG CCU CCC AUC CUG UAG GUC ACU G            |
| 2   | 6 H3D (+46-21)       | CUU CGA GGA GGU CUA GGA GGC GCC UC           |
| 2   | 7 H3A(+30+50)        | CUC CCA UCC UGU AGG UCA CUG                  |
| 21  | H3D(+19-03)          | UAC CAG UUU UUG CCC UGU CAG G                |
| 25  | 9 H3A (-06+20)       | UCA AUA UGC UGC UUC CCA AAC UGA AA           |
| 30  | H3A(+37+61)          | CUA GGA GGC GCC UCC CAU CCU GUA G            |
| 31  | H5A(+20+50)          | UUA UGA UUU CCA UCU ACG AUG UCA GUA          |
| 32  | H5D (+25-05)         | CUU ACC UGC CAG UGG AGG AUU AUA UUC          |
| 33  | H5D(+10-15)          | CAU CAG GAU UCU UAC CUG CCA GUG G            |
| 34  | H5A(+10+34)          | CGA UGU CAG UAC UUC CAA UAU UCA C            |
| 35  | H5D (-04-21)         | ACC AUU CAU CAG GAU UCU                      |
| 36  | H5D (+16-02)         | ACC UGC CAG UGG AGG AUU                      |
| 37  | H5A (-07+20)         | CCA AUA UUC ACU AAA UCA ACC UGU UAA          |
| 38  | H5D (+18-12)         | CAG GAU UGU UAC CUG CCA GUG GAG GAU UAU      |
| 39  | H5A(+05+35)          | ACG AUG UCA GUA CUU CCA AUA UUC ACU          |
| 40  | H5A(+15+45)          | AUU UCC AUC UAC GAU GUC AGU ACU UCC<br>AAU A |
| 41  | H10A(-05+16)         | CAG GAG CUU CCA AAU GCU GCA                  |
| 42  | H10A(-05+24)         | CUU GUC UUC AGG AGC UUC CAA AUG CUG CA       |
| 43  | H10A(+98+119)        | UCC UCA GCA GAA AGA AGC CAC G                |
| 44  | H10A(+130+149)       | UUA GAA AUC UCU CCU UGU GC                   |
| 45  | H10A(-33-14)         | UAA AUU GGG UGU UAC ACA AU                   |
| 46  | H11D(+26+49)         | CCC UGA GGC AUU CCC AUC UUG AAU              |
| 47  | H11D(+11-09)         | AGG ACU UAC UUG CUU UGU UU                   |
| 48  | H11A(+118+140)       | CUU GAA UUU AGG AGA UUC AUC UG               |
| 49  | H11A(+75+97)         | CÂU CUU CUG AUA AUU UUC CUG UU               |
| 50  | H12A(+52+75)         | UCU UCU GUU UUU GUU AGC CAG UCA              |
| 51  | H12A(-10+10)         | UCU AUG UAA ACU GAA AAU UU                   |
| 52  |                      | UUC UGG AGA UCC AUU AAA AC                   |
|     |                      | CAG CAG UUG CGU GAU CUC CAC UAG              |
| 54  |                      | UUC AUC AAC UAC CAC CAC CAU                  |
|     | Mary and and William | CUA AGC AAA AUA AUC UGA CCU UAA G            |
| 55  |                      | CUU GUA AAA GAA CCC AGC GGU CUU COG U        |
| 56  | H14A(+37+64)         | CON CON WAY OUR SEC 199                      |

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### TABLE 1A-continued

Description of 2'-0-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-0-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ | ID SEQUENCE    | NUCLEOTIDE SEQUENCE (5'-3')                  |
|-----|----------------|--|
| 57  | H14A(+14+35)   | CAU CUA CAG AUG UUU GCC CAU C                |
| 58  | H14A(+51+73)   | GAA GGA UGU CUU GUA AAA GAA CC               |
| 59  | H14D(-02+18)   | ACC UGU UCU UCA GUA AGA CG                   |
| 60  | H14D(+14-10)   | CAU GAC ACA CCU GUU CUU CAG UAA              |
| 61  | H14A(+61+80)   | CAU UUG AGA AGG AUG UCU UG                   |
| 62  | H14A(-12+12)   | AUC UCC CAA UAC CUG GAG AAG AGA              |
| 63  | H15A(-12+19)   | GCC AUG CAC UAA AAA GGC ACU GCA AGA          |
| 64  | H15A(+48+71)   | UCU UUA AAG CCA GUU GUG UGA AUC              |
| 65  | H15A(+08+28)   | UUU CUG AAA GCC AUG CAC UAA                  |
| 66  | H15D(+17-08)   | GUA CAU ACG GCC AGU UUU UGA AGA C            |
| 67  | H16A(-12+19)   | CUA GAU CCG CUU UUA AAA CCU GUU AAA          |
| 68  | H16A(-06+25)   | UCU UUU CUA GAU CCG CUU UUA AAA CCU<br>GUU A |
| 69  | H16A(-06+19)   | CUA GAU CCG CUU UUA AAA CCU GUU A            |
| 70  | H16A(+87+109)  | CCG UCU UCU GGG UCA CUG ACU UA               |
| 71  | H16A(-07+19)   | CUA GAU CCG CUU UUA AAA CCU GUU AA           |
| 72  | H16A(-07+13)   | CCG CUU UUA AAA CCU GUU AA                   |
| 73  | H16A(+12+37)   | UGG ADU GCU UUU UCU UUU CUA GAU CC           |
| 74  | H16A(+92+116)  | CAU GCU UCC GUC UUC UGG GUC ACU G            |
| 75  | H16A(+45+67)   | G AUC UUG UUU GAG UGA AUA CAG U              |
| 76  | H16A(+105+126) | GUU AUC CAG CCA UGC UUC CGU C                |
| 77  | H16D(+05-20)   | UGA UAA UUG GUA UCA CUA ACC UGU G            |
| 78  | H16D(+12-11)   | GUA UCA CUA ACC UGU GCU GUA C                |
| 79  | H19A(+35+53)   | CUG CUG GCA UCU UGC AGU U                    |
| 30  | H19A(+35+65)   | GCC UGA GCU GAU CUG CUG GCA UCU UGC<br>AGU U |
| 31  | H20A(+44+71)   | CUG GCA GAA UUC GAU CCA CCG GCU GUU C        |
| 32  | H20A(+147+168) | CAG CAG UAG UUG UCA UCU GCU C                |
| 33  | H20A(+185+203) | UGA UGG GGU GGU GGG UUG G                    |
| 14  | H20A(-08+17)   | AUC UGC AUU AAC ACC CUC UAG AAA G            |
| 5   | H20A(+30+53)   | CCG GCU GUU CAG UUG UUC UGA GGC              |
|     |                | AUC UGC AUU AAC ACC CUC UAG AAA GAA A        |
|     |                | GAA GGA GAA GAG AUU CUU ACC UUA CAA A        |
|     |                | AUU CGA UCC ACC GGC UGU UC                   |
|     |                | CAG CAG UAG UUG UCA UCU GC                   |

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### TABLE 1A-continued

Description of 2'-0-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-0-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ | ID SEQUENCE    | NU  | CLEC  | TIDE  | SEQ   | UENCE | (5  | -31 | 1.1 |     |   |
|-----|----------------|-----|-------|-------|-------|-------|-----|-----|-----|-----|---|
| 90  | H21A(-06+16)   |     |       |       |       | U CAU |     |     |     |     | - |
| 91  | H21A(+85+106)  |     |       |       |       | A ACA |     |     |     |     |   |
| 92  | H21A(+85+108)  |     |       |       |       | G GAA |     |     |     |     |   |
| 93  | H21A(+08+31)   |     |       |       |       | 3 AUA |     |     |     | A   |   |
| 94  | H21D(+18-07)   | UA  | c uu  | A CUC | g uct | J GUA | GCU | CUU | UCI | 1   |   |
| 95  | H22A(+22+45)   |     |       |       |       | ı ccu |     |     |     |     |   |
| 96  | H22A(+125+106) | CU  | G CA  | A UUC | ccc   | GAG   | ucu | CUG | C   |     |   |
| 97  | H22A(+47+69)   | ACI | J GC  | U GGA | ccc   | AUG   | UCC | UGA | UG  |     |   |
| 98  | H22A(+80+101)  | CU  | A AGI | U UGA | GGU   | AUG   | GAG | AGU |     |     |   |
| 99  | H22D(+13-11)   | UAU | J UC  | CAG   | ACC   | UGC   | AAU | UCC | cc  |     |   |
| 100 | H23A(+34+59)   | ACA | GUC   | g GUG | CUG   | AGA   | UAG | UAU | AGG | cc  |   |
| 101 | H23A(+18+39)   | UAC | GCC   | ACU   | UUG   | UUG   | CUC | UUG | c   |     |   |
| 102 | H23A(+72+90)   | מטט | AGA   | GGG   | CGC   | טסט   | CUU | c   |     |     |   |
| 103 | H24A(+48+70)   | GGG | CAC   | GCC   | AUU   | CCU   | ccu | UCA | GA  |     |   |
| 104 | H24A(-02+22)   | UCU | UCA   | GGG   | טטט   | GUA   | UGU | GAU | UCU |     |   |
| 105 | H25A(+9+36)    | CUG | GGC   | UGA   | AUU   | GUC   | UGA | AUA | UCA | CUG |   |
| 106 | H25A(+131+156) | CUG | UUG   | GCA   | CAU   | GUG   | AUC | CCA | CUG | AG  |   |
| 107 | H25D(+16-08)   | GUC | UAU   | ACC   | UGU   | UGG   | CAC | AUG | UGA |     |   |
| 108 | H26A(+132+156) | UGC | טטט   | CUG   | UAA   | ouc   | AUC | UGG | AGU | U   |   |
| 109 | H26A(-07+19)   | ccu | CCU   | uuc   | UGG   | CAU   | AGA | CCU | UCC | AC  |   |
| 110 | H26A(+68+92)   | UGU | GUC   | AUC   | CAU   | UCG   | UGC | AUC | מכט | G   |   |
| 111 | H27A(+82+106)  | UUA | AGG   | CCU   | CUU   | GUG   | CUA | CAG | GUG | G   |   |
| 112 | H27A(-4+19)    | GGG | GCU   | cuu   | CUU   | UAG   | cuc | UCU | GA  |     |   |
| 113 | H27D(+19-03)   | GAC | UUC   | CAA   | AGU   | CUU   | GCA | טטט | c   |     |   |
| 114 | H28A(-05+19)   | GCC | AAC   | AUG   | ccc   | AAA   | CUU | CCA | AAG |     |   |
| 115 | H28A(+99+124)  | CAG | AGA   | טטט   | CCU   | CAG   | CUC | CGC | CAG | GA  |   |
| 116 | H28D(+16-05)   | cuu | ACA   | ucu   | AGC   | ACC   | UCA | GAG |     |     |   |
| 117 | H29A(+57+81)   | UCC | GCC   | AUC   | UGU   | UAG   | GGU | CUG | UGC | C   |   |
| 119 | H29A(+18+42)   | AUU | UGG   | GUU   | AUC   | cuc   | UGA | AUG | UCG | C   |   |
| 119 | H29D(+17-05)   | CAU | ACC   | UCU   | UCA   | UGU   | AGU | ucc | C   |     |   |
| 120 | H30A(+122+147) | CAU | UUG   | AGC   | UGC   | GUC   | CAC | CUU | GUC | UG  |   |
|     | H30A(+25+50)   |     |       |       |       |       |     |     |     |     |   |
| 122 | H30D(+19-04)   | UUG | ccu   | GGG   | CUU   | CCU   | GAG | GCA | טט  |     |   |
| 123 | H31D(+06-18)   | DUC | UGA   | AAU   | AAC   | AUA   | UAC | CUG | UGC |     |   |
|     | H31D(+03-22)   |     |       |       |       |       |     |     |     |     |   |

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### TABLE 1A-continued

Description of 2'-O-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ | ID SEQUENCE    | NUCLEOTIDE SEQUENCE (5'-3')              |      |
|-----|----------------|--|------|
| 125 | 5 H31A(+05+25) | GAC UUG UCA AAU CAG AUU GGA              | _    |
| 126 | 6 H31D(+04-20) | GUU UCU GAA AUA ACA UAU ACC UGU          |      |
| 127 | 7 H32D(+04-16) | CAC CAG AAA UAC AUA CCA CA               |      |
| 128 | H32A(+151+170) |  |      |
| 125 | H32A(+10+32)   | CGA AAC UUC AUG GAG ACA UCU UG           |      |
| 130 | H32A(+49+73)   |  |      |
| 131 | H33D(+09-11)   | CAU GCA CAC ACC UUU GCU CC               |      |
| 132 | H33A(+53+76)   | UCU GUA CAA UCU GAC GUC CAG UCU          |      |
| 133 | H33A(+30+56)   | GUC UUU AUC ACC AUU UCC ACU UCA G        | :20  |
| 134 | H33A(+64+88)   | CCG UCU GCU UUU UCU GUA CAA UCU G        |      |
| 135 | H34A(+83+104)  | UCC AUA UCU GUA GCU GCC AGC C            |      |
| 136 | H34A(+143+165) |  |      |
| 137 | H34A(-20+10)   | UUU CUG UUA CCU GAA AAG AAU UAU A        | TITA |
|     |                | GAA                                      |      |
| 138 | H34A(+46+70)   | CAU UCA UUU CCU UUC GCA UCU UAC G        | 1    |
| 139 | H34A(+95+120)  | UGA UCU CUU UGU CAA UUC CAU AUC U        | G    |
| 140 | H34D(+10-20)   | UUC AGU GAU AUA GGU UUU ACC UUU C<br>CAG | cc   |
| 141 | H34A(+72+96)   | CUG UAG CUG CCA GCC AUU CUG UCA A        | G    |
| 142 | H35A(+141+161) | UCU UCU GCU CGG GAG GUG ACA              |      |
| 143 | H35A(+116+135) | CCA GUU ACU AUU CAG AAG AC               |      |
| 144 | H35A(+24+43)   | UCU UCA GGU GCA CCU UCU GU               |      |
| 145 | H36A(+26+50)   | UGU GAU GUG GUC CAC AUU CUG GUC A        |      |
| 146 | H36A(-02+18)   | CCA UGU GUU UCU GGU AUU CC               |      |
| 147 | H37A(+26+50)   | CGU GUA GAG UCC ACC UUU GGG CGU A        |      |
| 148 | H37A(+82+105)  | UAC UAA UUU CCU GCA GUG GUC ACC          |      |
| 149 | H37A(+134+157) | UUC UGU GUG AAA UGG CUG CAA AUC          |      |
| 150 | H39A(-01+19)   | CCU UCA AAG GAA UGG AGG CC               |      |
| 151 | H38A(+59+83)   | UGC UGA AUU UCA GCC UCC AGU GGU U        |      |
| 152 | H38A(+88+112)  | UGA AGU CUU CCU CUU UCA GAU UCA C        |      |
|     |                | CUG GCU UUC UCU CAU CUG UGA UUC          |      |
|     |                | GUU GUA AGU UGU CUC CUC UU               |      |
| 155 | H39A(+102+121) | UUG UCU GUA ACA GCU GCU GU               |      |
|     |                | GCU CUA AUA CCU UGA GAG CA               |      |
|     | H40A(-05+17)   | CUU UGA GAC CUC AAA UCC UGU U            |      |
|     |                | CUU UAU UUU CCU UUC AUC UCU GGG C        |      |
|     |                |  |      |

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## TABLE 1A-continued

Description of 2'-0-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-0-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ | ID SEQUENCE                | NUCLEOTIDE SEQUENCE (5'-3')                        |   |
|-----|----------------------------|--|---|
| 15  | 9 H42A(-04+23)             | AUC GUU UCU UCA CGG ACA GUG UGC UGG                | - |
| 16  | 0 H42A(+86+109)            |  |   |
| 16  | 1 H42D(+19-02)             | A CCU UCA GAG GAC UCC UCU UGC                      |   |
| 16  | 2 H43D(+10-15)             |  |   |
| 163 | 3 H43A(+101+120)           |  |   |
| 164 | H43A(+78+100)              | UCA CCC UUU CCA CAG GCG UUG CA                     |   |
| 169 | 5 H44A(+85+104)            |  |   |
| 166 | H44D(+10-10)               | AAA GAC UUA CCU UAA GAU AC                         |   |
| 167 | H44A(-06+14)               | AUC UGU CAA AUC GCC UGC AG                         |   |
| 168 | H46D(+16-04)               | UUA CCU UGA CUU GCU CAA GC                         |   |
| 169 | H46A(+90+109)              | UCC AGG UUC AAG UGG GAU AC                         |   |
| 170 | H47A(+76+100)              | GCU CUU CUG GGC UUA UGG GAG CAC U                  |   |
| 171 | H47D(+25-02)               | ACC UUU AUC CAC UGG AGA UUU GUC UGC                |   |
| 172 | H47A(-9+12)                | UUC CAC CAG UAA CUG AAA CAG                        |   |
| 173 | H50A(+02+30)               | CCA CUC AGA GCU CAG AUC UUC UAA CUU C              | C |
| 174 | H50A(+07+33)               | CUU CCA CUC AGA GCU CAG AUC UUC UAA                | 2 |
| 175 | H50D(+07-18)               | GGG AUC CAG UAU ACU UAC AGG CUC C                  |   |
| 176 | H51A(-01+25)               | ACC AGA GUA ACA GUC UGA GUA GGA GC                 |   |
| 177 | H51D(+16-07)               | CUC AUA CCU UCU GCU UGA UGA UC                     |   |
| 178 | H51A(+111 +134)            | UUC UGU CCA AGC CCG GUU GAA AUC                    |   |
| 179 | H51A(+61+90)               | ACA UCA AGG AAG AUG GCA UUU CUA GUU<br>UGG         |   |
| 180 | H51A(+66+90)               | ACA UCA AGG AAG AUG GCA UUU CUA G                  |   |
| 181 | H51A(+66+95)               | CUC CAA CAU CAA GGA AGA UGG CAU UUC<br>UAG         |   |
| 182 | H51D(+08-17)               | AUC AUU UUU UCU CAU ACC UUC UGC U                  |   |
| 183 | H51A/D(+08-17)<br>& (-15+) | AUC AUU UUU UCU CAU ACC UUC UGC UAG<br>GAG CUA AAA |   |
| 184 | H51A(+175+195)             | CAC CCA CCA UCA CCC UCU GUG                        |   |
| 185 | H51A(+199+220)             | AUC AUC UCG UUG AUA UCC UCA A                      |   |
| 186 | H52A(-07+14)               | UCC UGC AUU GUU GCC UGU AAG                        |   |
| 187 | H52A(+12+41)               | UCC AAC UGG GGA CGC CUC UGU UCC AAA                |   |
| 188 | H52A(+17+37)               | ACU GGG GAC GCC UCU GUU CCA                        |   |
| 89  | H52A(+93+112)              | CCG UAA UGA UUG UUC UAG CC                         |   |
| 90  | H52D(+05-15)               | UGU UAA AAA ACU UAC UUC GA                         |   |
|     |                            | CAU UCA ACU GUU GCC UCC GGU UCU G                  |   |

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## TABLE 1A-continued

Description of 2'-0-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-0-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

| SEQ : | ID SEQUENCE    | NUC        | CLEO' | FIDE |     |     |       |       |     |     |   |
|-------|----------------|------------|-------|------|-----|-----|-------|-------|-----|-----|---|
| 192   | H53A(+39+62)   | 100        | G UU  |      |     |     |       |       |     | 3   |   |
| 193   | H53A(+39+69)   | CAU        | J UCA |      |     |     |       |       |     |     | A |
| 194   | H53D(+14-07)   | UAC        | UA    | CCU  | UGG | יטט | J CUC | G UGA |     |     |   |
| 195   | H53A(+23+47)   | CUC        | AAC   | GUG  | טטט | טטט | UAC   | י טטט | AUC | c   |   |
| 196   | H53A(+150+176) | UGU        | AUA   | GGG  | ACC | CUC | CUL   | CCA   | UGA | CUC |   |
| 197   | H53D(+20-05)   | CUA        | ACC   | uug  | GUU | טכט | GUG   | AUU   | טטט | u   |   |
| 198   | H53D(+09-18)   | GGU        | AUC   | יטטט | GAU | ACU | AAC   | cuu   | GGU | טטט |   |
| 199   | H53A(-12+10)   | AUU        | CUU   | UCA  | ACU | AGA | AUA   | AAA   | G   |     |   |
| 200   | H53A(-07+18)   | GAU        | UCU   | GAA  | טטכ | טטט | CAA   | CUA   | GAA | U   |   |
| 201   | H53A(+07+26)   | AUC        | CCA   | CUG  | AUU | CUG | AAU   | UC    |     |     |   |
| 202   | H53A(+124+145) | UUG        | GCU   | CUG  | GCC | UGU | ccu   | AAG   | Ā   |     |   |
| 203   | H46A(+86+115)  | CUC        | טטט   | ucc  | AGG | nnc | AAG   | UGG   | GAU | ACU |   |
| 204   | H46A(+107+137) | CAA        |       | מטט  | CUU | UUA | GUU   | GCU   | GÇU | CUU |   |
| 205   | H46A(-10+20)   | UAU<br>AAG | UCU   | טטט  | GUU | CUU | CUA   | GCC   | UGG | AGA |   |
| 06    | H46A(+50+77)   | CUG        | cuu   | CCU  | CCA | ACC | AUA   | AAA   | CAA | AUU | C |
| 07    | H45A(-06+20)   | CCA        | AUG   | CCA  | UCC | UGG | AGU   | UCC   | UGU | AA  |   |
| 08    | H45A(+91 +110) | UCC        | UGU   | AGA  | AUA | CUG | GCA   | UC    |     |     |   |
| 09    | H45A(+125+151) | UGC        | AGA   | cca  | CCU | GCC | ACC   | GCA   | GAU | UCA |   |
| 10    | H45D(+16 -04)  | CUA        | CCU   | CDD  | טטט | UCU | GUC   | UG    |     |     |   |
| 11    | H45A(+71+90)   | UGU        | טטט   | UGA  | GGA | UUG | CUG   | AA    |     |     |   |

#### TABLE 1B

Description of a cocktail of 2'-0-methyl phosphorothicate antisense oligonuclectides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

| SEQ | SEQUENCE                     | NUC | LEOT     | IDE | SEQU | ENCE | (5) | -3 -) |     | 55 |
|-----|------------------------------|-----|----------|-----|------|------|-----|-------|-----|----|
| 91  | H20A(+44+71)                 | CUG | GCA      | GAA | UUC  | GAU  | CCA | CCG   | GCU |    |
| 82  | H20A(+147+168)               | GUU | C        | UAG |      |      |     |       |     | 60 |
| 80  | H19A(+35+65)<br>H20A(+44+71) | GCC | UGA      | GCU | GAU  | CUG  | CUG | GCA   | UCU |    |
| 82  | H20A(+147+168)               | AGU | U<br>GCA | GAA | UUC  | GAU  | CCA | CCG   | GCU | 65 |
|     |                              | GUU | C<br>CAG | UAG | UUG  | UCA  | UCU | GCU   | C   | 00 |

#### TABLE 1B-continued

Description of a cocktail of 2'-0-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

|   | ID  | SEQUENCE       | NUC | LEOT | IDE : | SEQU | ENCE | (5) | -3() |     |
|---|-----|----------------|-----|------|-------|------|------|-----|------|-----|
| 0 | 194 | H53D(+14-07)   | UAC | UAA  | ccu   | UGG  | טטט  | CUG | UGA  |     |
|   | 195 | H53A(+23+47)   | CUG | AAG  | GUG   | UUC  | UUG  | UAC | UUC  |     |
|   |     |                | AUC | C    |       |      |      |     |      |     |
|   | 196 | H53A(+150+175) | UGU | AUA  | GGG   | ACC  | CUC  | CUU | CCA  | UGA |
| 5 |     |                | CUC |      |       |      |      |     |      |     |

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TABLE 1C

Description of a "weasel" of 2'-0-methyl phosphorothicate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

| SEQ | SEQUENCE               | NUCLEOTIDE SEQUENCE (5'-3')                 |
|-----|------------------------|---|
| 81  | H20A(+44+71) -         | CUG GCA GAA UUC GAU CCA CCG GCU GUU C-      |
| 82  | H20A(+147+168)         | CAG CAG UAG UUG UCA UCU GCU C               |
|     |                        | GCC UGA GCU GAU CUG CUG GCA UCU UGC         |
| 88  | H20A(+44+63) -         | -AUU CGA UCC ACC GGC UGU UC-                |
| 79  | H20A(+149+168)         | CUG CUG GCA UCU UGC AGU U                   |
|     |                        | GCC UGA GCU GAU CUG CUG GCA UCU UGC         |
| 88  | H20A(+44+63)           | -AUU CGA UCC ACC GGC UGU UC-                |
| B0  | H19A(+35+65)-          | GCC UGA GCU GAU CUG CUG GCA UCU UGC         |
| 79  | H20A(+149+168)         | -CUG CUG GCA UCU UGC AGU U                  |
| 138 | H34A(+46+70) -         | CAU UCA DUU CCU UUC GCA UCU UAC G-          |
| 139 | H34A(+94+120)          | UGA UCU CUU UGU CAA DUC CAU AUC UG          |
|     | H31D(+03-22)-<br>UU-   | UAG UUU CUG AAA UAA CAU AUA CCU G-          |
| 144 | H35A(+24+43)           | UCU UCA GGU GCA CCU UCU GU                  |
|     | AA-                    | CUG AAG GUG UUC UUG UAC UUC AUC C-          |
|     | H53A(+150+175)-<br>AA- | UGU AUA GGG ACC CUC CUU CCA UGA CUC-<br>AA- |
| 194 | H53D(+14-07)           | UAC UAA CCU UGG UUU CUG UGA                 |
| _ , | Aimed at exons         | CAG CAG UAG UUG UCA UCU GCU CAA CUG         |
| 212 | 19/20/20               | GCA GAA UUC GAU CCA CCG GCU GUU CAA         |
|     |                        | GCC UGA GCU GAU CUG CUC GCA UCU<br>UGC AGU  |

## DETAILED DESCRIPTION OF THE INVENTION

General

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variation and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally equivalent products, compositions and methods are clearly within the scope of the invention as described herein.

Sequence identity numbers (SEQ ID NO:) containing nucleotide and amino acid sequence information included in this specification are collected at the end of the description and have been prepared using the programme Patent In Version 3.0. Each nucleotide or amino acid sequence is identified in the sequence listing by the numeric indicator <210> followed by the sequence identifier (e.g. <210>1, <210>2, etc.). The length, type of sequence and source organism for each nucleotide or amino acid sequence are indicated by information provided in the numeric indicator 65 fields <211>, <212> and <213>, respectively. Nucleotide and amino acid sequences referred to in the specification are

defined by the information provided in numeric indicator field <400> followed by the sequence identifier (e.g. <400>1, <400>2, etc.).

An antisense molecules nomenclature system was proposed and published to distinguish between the different antisense molecules (see Mann et al., (2002) *J Gen Med* 4, 644-654). This nomenclature became especially relevant when testing several slightly different antisense molecules, all directed at the same target region, as shown below:

H#A/D(x:y).

The first letter designates the species (e.g. H: human, M: 50 murine, C: canine) "#" designates target dystrophin exon number.

"A/D" indicates acceptor or donor splice site at the beginning and end of the exon, respectively.

(x y) represents the annealing coordinates where "-" or "+" indicate intronic or exonic sequences respectively. As an example, A(-6+18) would indicate the last 6 bases of the intron preceding the target exon and the first 18 bases of the target exon. The closest splice site would be the acceptor so these coordinates would be preceded with an "A". Describing annealing coordinates at the donor splice site could be D(+2-18) where the last 2 exonic bases and the first 18 intronic bases correspond to the annealing site of the antisense molecule. Entirely exonic annealing coordinates that would be represented by A(+65+85), that is the site between the 65th and 85th nucleotide from the start of that exon.

The entire disclosures of all publications (including patents, patent applications, journal articles, laboratory manu-

als, books, or other documents) cited herein are hereby incorporated by reference. No admission is made that any of the references constitute prior art or are part of the common general knowledge of those working in the field to which this invention relates.

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As used necessarily herein the term "derived" and "derived from" shall be taken to indicate that a specific integer may be obtained from a particular source albeit not directly from that source.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Other definitions for selected terms used herein may be 15 found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

## DESCRIPTION OF THE PREFERRED EMBODIMENT

When antisense molecule(s) are targeted to nucleotide 25 sequences involved in splicing in exons within pre-mRNA sequences, normal splicing of the exon may be inhibited causing the splicing machinery to by-pass the entire mutated exon from the mature mRNA. The concept of antisense oligonucleotide induced exon skipping is shown in FIG. 2. 30 In many genes, deletion of an entire exon would lead to the production of a non-functional protein through the loss of important functional domains or the disruption of the reading frame. In some proteins, however, it is possible to shorten the protein by deleting one or more exons, without 35 disrupting the reading frame, from within the protein without seriously altering the biological activity of the protein. Typically, such proteins have a structural role and or possess functional domains at their ends. The present invention describes antisense molecules capable of binding to specified dystrophin pre-mRNA targets and re-directing processing of that gene.

Antisense Molecules

According to a first aspect of the invention, there is provided antisense molecules capable of binding to a 4s selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules are preferably selected from the group of compounds shown in Table 1A. There is also provided a combination or "cocktail" of two or more antisense oligonucleotides capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules in a "cocktail" are preferably selected from the group of compounds shown in Table 1B. Alternatively, exon skipping may 55 be induced by antisense oligonucleotides joined together "weasels" preferably selected from the group of compounds shown in Table 1C.

Designing antisense molecules to completely mask consensus splice sites may not necessarily generate any skipping of the targeted exon. Furthermore, the inventors have discovered that size or length of the antisense oligonucleotide itself is not always a primary factor when designing antisense molecules. With some targets such as exon 19, antisense oligonucleotides as short as 12 bases were able to induce exon skipping, albeit not as efficiently as longer (20-31 bases) oligonucleotides. In some other targets, such

as murine dystrophin exon 23, antisense oligonucleotides only 17 residues long were able to induce more efficient skipping than another overlapping compound of 25 nucleotides.

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The inventors have also discovered that there does not appear to be any standard motif that can be blocked or masked by antisense molecules to redirect splicing. In some exons, such as mouse dystrophin exon 23, the donor splice site was the most amenable to target to re-direct skipping of that exon. It should be noted that designing and testing a series of exon 23 specific antisense molecules to anneal to overlapping regions of the donor splice site showed considerable variation in the efficacy of induced exon skipping. As reported in Mann et al., (2002) there was a significant variation in the efficiency of bypassing the nonsense mutation depending upon antisense oligonucleotide annealing ("Improved antisense oligonucleotide induced exon skipping in the mdx mouse model of muscular dystrophy". J Gen Med 4: 644-654). Targeting the acceptor site of exon 23 or several internal domains was not found to induce any consistent exon 23 skipping.

In other exons targeted for removal, masking the donor splice site did not induce any exon skipping. However, by directing antisense molecules to the acceptor splice site (liuman exon 8 as discussed below), strong and sustained exon skipping was induced. It should be noted that removal of human exon 8 was tightly linked with the co-removal of exon 9. There is no strong sequence homology between the exon 8 antisense oligonucleotides and corresponding regions of exon 9 so it does not appear to be a matter of cross reaction. Rather the splicing of these two exons is inextricably linked. This is not an isolated instance as the same effect is observed in canine cells where targeting exon 8 for removal also resulted in the skipping of exon 9. Targeting exon 23 for removal in the mouse dystrophin pre-mRNA also results in the frequent removal of exon 22 as well. This effect occurs in a dose dependent manner and also indicates close coordinated processing of 2 adjacent exons.

In other targeted exons, antisense molecules directed at the donor or acceptor splice sites did not induce exon skipping while annealing antisense molecules to intra-exonic regions (i.e. exon splicing enhancers within human dystrophin exon 6) was most efficient at inducing exon skipping. Some exons, both mouse and human exon 19 for example, are readily skipped by targeting antisense molecules to a variety of motifs. That is, targeted exon skipping is induced after using antisense oligonucleotides to mask donor and acceptor splice sites or exon splicing enhancers.

To identify and select antisense oligonucleotides suitable for use in the modulation of exon skipping, a nucleic acid sequence whose function is to be modulated must first be identified. This may be, for example, a gene (or mRNA transcribed form the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (i.e. splice donor sites, splice acceptor sites, or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

Preferably, the present invention aims to provide antisense molecules capable of binding to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping. Duchenne muscular dystrophy arises from mutations that preclude the synthesis of a functional dystrophin gene product. These Duchenne muscular dystrophy

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gene defects are typically nonsense mutations or genomic rearrangements such as deletions, duplications or microdeletions or insertions that disrupt the reading frame. As the human dystrophin gene is a large and complex gene with the 79 exons being spliced together to generate a mature mRNA 5 with an open reading frame of approximately 11,000 bases, there are many positions where these mutations can occur. Consequently, a comprehensive antisense oligonucleotide based therapy to address many of the different disease-causing mutations in the dystrophin gene will require that 10 many exons can be targeted for removal during the splicing process.

Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (i.e. splice donor sites, splice acceptor sites or exonic splicing enhancer 15 elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

The oligonucleotide and the DNA or RNA are complementary to each other when a sufficient number of corre- 20 sponding positions in each molecule are occupied by nucleotides which can hydrogen bond with each other. Thus, "specifically hybridisable" and "complementary" are terms which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific 25 binding occurs between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an antisense molecule need not be 100% complementary to that of its target sequence to be specifically hybridisable. An antisense molecule is specifically hybridisable when binding 30 of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target sequences under condi- 35 tions in which specific binding is desired, i.e., under physiological conditions in the case of in vivo assays or therapeutic treatment, and in the case of in vitro assays, under conditions in which the assays are performed.

While the above method may be used to select antisense 40 molecules capable of deleting any exon from within a protein that is capable of being shortened without affecting its biological function, the exon deletion should not lead to a reading frame shift in the shortened transcribed mRNA. Thus, if in a linear sequence of three exons the end of the 45 first exon encodes two of three nucleotides in a codon and the next exon is deleted then the third exon in the linear sequence must start with a single nucleotide that is capable of completing the nucleotide triplet for a codon. If the third exon does not commence with a single nucleotide there will 50 be a reading frame shift that would lead to the generation of truncated or a non-functional protein.

containing the oligonucleotide as one member thereof, which structural modification does not substantially hinder the end of a codon, consequently there may be a need to delete more than one exon from the pre-mRNA to ensure in-frame reading of the mRNA. In such circumstances, a plurality of antisense oligonucleotides may need to be selected by the method of the invention wherein each is directed to a different region responsible for inducing splication in the exons that are to be deleted.

The length of an antisense molecule may vary so long as it is capable of binding selectively to the intended location within the pre-mRNA molecule. The length of such sequences can be determined in accordance with selection 65 procedures described herein. Generally, the antisense molecule will be from about 10 nucleotides in length up to about

50 nucleotides in length. It will be appreciated however that any length of nucleotides within this range may be used in the method. Preferably, the length of the antisense molecule is between 17 to 30 nucleotides in length.

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In order to determine which exons can be connected in a dystrophin gene, reference should be made to an exon boundary map. Connection of one exon with another is based on the exons possessing the same number at the 3' border as is present at the 5' border of the exon to which it is being connected. Therefore, if exon 7 were deleted, exon 6 must connect to either exons 12 or 18 to maintain the reading frame. Thus, antisense oligonucleotides would need to be selected which redirected splicing for exons 7 to 11 in the first instance or exons 7 to 17 in the second instance. Another and somewhat simpler approach to restore the reading frame around an exon 7 deletion would be to remove the two flanking exons. Induction of exons 6 and 8 skipping should result in an in-frame transcript with the splicing of exons 5 to 9. In practise however, targeting exon 8 for removal from the pre-mRNA results in the co-removal of exon 9 so the resultant transcript would have exon 5 joined to exon 10. The inclusion or exclusion of exon 9 does not alter the reading frame. Once the antisense molecules to be tested have been identified, they are prepared according to standard techniques known in the art. The most common method for producing antisense molecules is the methylation of the 2' hydroxyribose position and the incorporation of a phosphorothioate backbone produces molecules that superficially resemble RNA but that are much more resistant to nuclease degradation.

To avoid degradation of pre-mRNA during duplex formation with the antisense molecules, the antisense molecules used in the method may be adapted to minimise or prevent cleavage by endogenous RNase H. This property is highly preferred as the treatment of the RNA with the unmethylated oligonucleotides either intracellularly or in crude extracts that contain RNase H leads to degradation of the pre-mRNA: antisense oligonucleotide duplexes. Any form of modified antisense molecules that is capable of by-passing or not inducing such degradation may be used in the present method. An example of antisense molecules which when duplexed with RNA are not cleaved by cellular RNase H is 2'-O-methyl derivatives. 2'-O-methyl-oligoribonucleotides are very stable in a cellular environment and in animal tissues, and their duplexes with RNA have higher Tm values than their ribo- or deoxyribo-counterparts.

Antisense molecules that do not activate RNase H can be made in accordance with known techniques (see, e.g., U.S. Pat. No. 5,149,797). Such antisense molecules, which may be deoxyribonucleotide or ribonucleotide sequences, simply contain any structural modification which sterically hinders or prevents binding of RNase H to a duplex molecule containing the oligonucleotide as one member thereof, which structural modification does not substantially hinder or disrupt duplex formation. Because the portions of the oligonucleotide involved in duplex formation are substantially different from those portions involved in RNase H binding thereto, numerous antisense molecules that do not activate RNase H are available. For example, such antisense all, of the inter-nucleotide bridging phosphate residues are modified phosphates, such as methyl phosphonates, methyl phosphorothioates, phosphoromorpholidates, ropiperazidates and phosphoramidates. For example, every other one of the internucleotide bridging phosphate residues may be modified as described. In another non-limiting example, such antisense molecules are molecules wherein at

least one, or all, of the nucleotides contain a 2' lower alkyl moiety (e.g., C<sub>1</sub>-C<sub>4</sub>, linear or branched, saturated or unsaturated alkyl, such as methyl, ethyl, ethenyl, propyl, 1-propenyl, 2-propenyl, and isopropyl). For example, every other one of the nucleotides may be modified as described.

While antisense oligonucleotides are a preferred form of the antisense molecules, the present invention comprehends other oligomeric antisense molecules, including but not limited to oligonucleotide mimetics such as are described below.

Specific examples of preferred antisense compounds useful in this invention include oligonucleotides containing modified backbones or non-natural inter-nucleoside linkages. As defined in this specification, oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their inter-nucleoside backbone can also be considered to be 20 oligonucleosides.

In other preferred oligonucleotide mimetics, both the sugar and the inter-nucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugarbackbone of an oligonucleotide is replaced with an amide 30 containing backbone, in particular an aminoethylglycine backbone. The nucleo-bases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone.

Modified oligonucleotides may also contain one or more 35 substituted sugar moieties. Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. Certain nucleo-bases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 40 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine. 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2° C. and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates that enhance the activity, 50 cellular distribution or cellular uptake of the oligonucleotide, Such moieties include but are not limited to lipid moieties such as a cholesterol moiety, cholic acid, a thiocher, e.g., hexyl-S-tritylthiol, a thiocholesterol, an aliphatic chain, e.g., dodecandiol or undecyl residues, a phospholipid, 55 e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety.

It is not necessary far all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes antisense compounds that are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this

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invention, are antisense molecules, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the increased resistance to nuclease degradation, increased cellular uptake, and an additional region for increased binding affinity for the target nucleic acid.

The antisense molecules used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). One method for synthesising oligonucleotides on a modified solid support is described in U.S. Pat. No. 4,458,066.

Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates—and alkylated derivatives. In one such automated embodiment, diethyl-phosphoramidites are used as starting materials and may be synthesized as described by Beaucage, et al., (1981) Tetrahedron Letters, 22:1859-1862.

The antisense molecules of the invention are synthesised in vitro and do not include antisense compositions of biological origin, or genetic vector constructs designed to direct the in vivo synthesis of antisense molecules. The molecules of the invention may also be mixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption.

Therapeutic Agents

The present invention also can be used as a prophylactic or therapeutic, which may be utilised for the purpose of treatment of a genetic disease.

Accordingly, in one embodiment the present invention provides antisense molecules that bind to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping described herein in a therapeutically effective amount admixed with a pharmaceutically acceptable carrier, diluent, or excipient.

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic or similarly untoward reaction, such as gastric upset and the like, when administered to a patient. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in Martin, Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, Pa., (1990).

In a more specific form of the invention there are provided pharmaceutical compositions comprising therapeutically effective amounts of an antisense molecule together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength and

additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol). The material may be incorporated into particulate 5 preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hylauronic acid may also be used. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Martin, Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 1435-1712 that are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilised form.

It will be appreciated that pharmaceutical compositions provided according to the present invention may be administered by any means known in the art. Preferably, the pharmaceutical compositions for administration are administered by injection, orally, or by the pulmonary, or nasal route. The antisense molecules are more preferably delivered by intravenous, intra-arterial, intraperitoneal, intramuscular, or subcutaneous routes of administration.

Antisense Molecule Based Therapy

Also addressed by the present invention is the use of 25 antisense molecules of the present invention, for manufacture of a medicament for modulation of a genetic disease.

The delivery of a therapeutically useful amount of antisense molecules may be achieved by methods previously published. For example, intracellular delivery of the antisense molecule may be via a composition comprising an admixture of the antisense molecule and an effective amount of a block copolymer. An example of this method is described in US patent application US 20040248833.

Other methods of delivery of antisense molecules to the 35 nucleus are described in Mann C J et al., (2001) ["Antisense-induced exon skipping and the synthesis of dystrophin in the mdx mouse". Proc., Natl. Acad. Science, 98(1) 42-47J and in Gebski et al., (2003). Human Molecular Genetics, 12(15): 1801-1811.

A method for introducing a nucleic acid molecule into a cell by way of an expression vector either as naked DNA or complexed to lipid carriers, is described in U.S. Pat. No. 6.806.084.

It may be desirable to deliver the antisense molecule in a 45 colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-inwater emulsions, micelles, mixed micelles, and liposomes or liposome formulations.

Liposomes are artificial membrane vesicles which are useful as delivery vehicles in vitro and in vivo. These formulations may have net cationic, anionic or neutral charge characteristics and are useful characteristics with in vitro, in vivo and ex vivo delivery methods. It has been 55 shown that large unilamellar vesicles (LUV), which range in size from 0.2-4.0. PHI.m can encapsulate a substantial percentage of an aqueous buffer containing large macromolecules. RNA, and DNA can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, et al., Trends Biochem. Sci., 6:77, 1981)

In order for a liposome to be an efficient gene transfer vehicle, the following characteristics should be present: (1) encapsulation of the antisense molecule of interest at high 65 efficiency while not compromising their biological activity; (2) preferential and substantial binding to a target cell in

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comparison to non-target cells; (3) delivery of the aqueous contents of the vesicle to the target cell cytoplasm at high efficiency; and (4) accurate and effective expression of genetic information (Mannino, et al., Biotechniques, 6:682, 1988).

The composition of the liposome is usually a combination of phospholipids, particularly high-phase-transition-temperature phospholipids, usually in combination with steroids, especially cholesterol. Other phospholipids or other lipids may also be used. The physical characteristics of liposomes depend on pH, ionic strength, and the presence of divalent cations.

Alternatively, the antisense construct may be combined with other pharmaceutically acceptable carriers or diluents to produce a pharmaceutical composition. Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. The composition may be formulated for parenteral, intramuscular, intravenous, subcutaneous, intraocular, oral or transdermal administration.

The routes of administration described are intended only as a guide since a skilled practitioner will be able to determine readily the optimum route of administration and any dosage for any particular animal and condition. Multiple approaches for introducing functional new genetic material into cells, both in vitro and in vivo have been attempted (Friedmann (1989) Science, 244:1275-1280).

These approaches include integration of the gene to be expressed into modified retroviruses (Friedmann (1989) supra; Rosenberg (1991) Cancer Research 51(18), suppl.: 5074S-5079S); integration into non-retrovirus vectors (Rosenfeld, et al. (1992) Cell, 68:143-155; Rosenfeld, et al. (1991) Science, 252:431-434); or delivery of a transgene linked to a heterologous promoter-enhancer element via liposomes (Friedmann (1989), supra; Brigham, et al. (1989) Am. J. Med. Sci., 298:278-281; Nabel, et al. (1990) Science. 249:1285-1288; Hazinski, et al. (1991) Am. J. Resp. Cell Molec. Biol., 4:206-209; and Wang and Huang (1987) Proc. Natl. Acad. Sci. (USA), 84:7851-7855); coupled to ligandspecific, cation-based transport systems (Wu and Wu (1988) J. Biol. Chem., 263:14621-14624) or the use of naked DNA. expression vectors (Nabel et al. (1990), supra); Wolff et al. (1990) Science, 247:1465-1468). Direct injection of transgenes into tissue produces only localized expression (Rosenfeld (1992) supra); Rosenfeld et al. (1991) supra; Brigham et al. (1989) supra; Nabel (1990) supra; and Hazinski et al. (1991) supra). The Brigham et al. group (Am. J. Med. Sci. (1989) 298:278-281 and Clinical Research (1991) 39 (abstract)) have reported in vivo transfection only of lungs of mice following either intravenous or intratracheal administration of a DNA liposome complex. An example of a review article of human gene therapy procedures is: Anderson, Science (1992) 256:808-813.

The antisense molecules of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to prodrugs and pharmaceutically acceptable salts of the compounds of the invention, pharmaceutically acceptable salts of such pro-drugs, and other bioequivalents.

The term "pharmaceutically acceptable salts" refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

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For oligonucleotides, preferred examples of pharmaceutically acceptable salts include but are not limited to (a) salts formed with cations such as sodium, potassium, ammonium, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (e) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, malefic 10 acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polygiutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine. The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is 20 desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including rectal delivery), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, (including by nebulizer, intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intra-arterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Oligonucleotides with at 30 least one 2'-O-methoxyethyl modification are believed to be particularly useful for oral administration.

The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Kits of the Invention

The invention also provides kits for treatment of a patient 45 with a genetic disease which kit comprises at least an antisense molecule, packaged in a suitable container, together with instructions for its use.

In a preferred embodiment, the kits will contain at least one antisense molecule as shown in Table 1A, or a cocktail of antisense molecules as shown in Table 1B or a "weasel" compound as shown in Table 1C. The kits may also contain peripheral reagents such as buffers, stabilizers, etc.

Those of ordinary skill in the field should appreciate that 55 applications of the above method has wide application for identifying antisense molecules suitable for use in the treatment of many other diseases.

#### EXAMPLES

The following Examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these Examples in no way serve to limit the true scope of this

invention, but rather are presented for illustrative purposes. The references cited herein are expressly incorporated by

Methods of molecular cloning, immunology and protein chemistry, which are not explicitly described in the following examples, are reported in the literature and are known by those skilled in the art. General texts that described conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art, included, for example: Sambrook et al, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (1989); Glover ed., DNA Cloning: A Practical Approach, Volumes 1 and 11, MRL Press, Ltd., Oxford, U.K. (1985); and Ausubel, E., Brent, R., Kingston, R. E., Moore, D. D., Seidman, J. G., Smith, J. A., Struhl, K. Current Protocols in Molecular Biology. Greene Publishing Associates/Wiley Intersciences, New York (2002).

#### Determining Induced Exon Skipping in Human Muscle Cells

Aftempts by the inventors to develop a rational approach in antisense molecules design were not completely successful as there did not appear to be a consistent trend that could be applied to all exons. As such, the identification of the most effective and therefore most therapeutic antisense molecules compounds has been the result of empirical studies.

These empirical studies involved the use of computer programs to identify motifs potentially involved in the splicing process. Other computer programs were also used to identify regions of the pre-mRNA which may not have had extensive secondary structure and therefore potential sites for annealing of antisense molecules. Neither of these approaches proved completely reliable in designing antisense oligonucleotides for reliable and efficient induction of exon skipping.

Annealing sites on the human dystrophin pre-mRNA were selected for examination, initially based upon known or predicted motifs or regions involved in splicing. 20Me antisense oligonucleotides were designed to be complementary to the target sequences under investigation and were synthesised on an Expedite 8909 Nucleic Acid Synthesiser. Upon completion of synthesis, the oligonucleotides were cleaved from the support column and de-protected in ammonium hydroxide before being desalted. The quality of the oligonucleotide synthesis was monitored by the intensity of the trityl signals upon each deprotection step during the synthesis as detected in the synthesis log. The concentration of the antisense oligonucleotide was estimated by measuring the absorbance of a diluted aliquot at 260 nm.

Specified amounts of the antisense molecules were then tested for their ability to induce exon skipping in an in vitro assay, as described below.

Briefly, normal primary myoblast cultures were prepared from human muscle biopsies obtained after informed consent. The cells were propagated and allowed to differentiate into myotubes using standard culturing techniques. The cells were then transfected with the antisense oligonucleotides by delivery of the oligonucleotides to the dells as cationic lipoplexes, mixtures of antisense molecules or cationic liposome preparations.

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The cells were then allowed to grow for another 24 hours, after which total RNA was extracted and molecular analysis commenced. Reverse transcriptase amplification (RT-PCR) was undertaken to study the targeted regions of the dystrophin pre-mRNA or induced exonic re-arrangements.

For example, in the testing of an antisense molecule for inducing exon 19 skipping the RT-PCR test scanned several exons to detect involvement of any adjacent exons. For example, when inducing skipping of exon 19, RT-PCR was 10 carried out with primers that amplified across exons 17 and 21. Amplifications of even larger products in this area (i.e. exons 13-26) were also carried out to ensure that there was minimal amplification bias for the shorter induced skipped transcript. Shorter or exon skipped products tend to be amplified more efficiently and may bias the estimated of the normal and induced transcript.

The sizes of the amplification reaction products were estimated on an agarose gel and compared against appropriate size standards. The final confirmation of identity of these products was carried out by direct DNA sequencing to establish that the correct or expected exon junctions have been maintained.

Once efficient exon skipping had been induced with one antisense molecule, subsequent overlapping antisense molccules may be synthesized and then evaluated in the assay as described above. Our definition of an efficient antisense skipping at 300 nM, a concentration some 15 fold higher than H8A(-06+18), which is the preferred antisense molecule.

This data shows that some particular antisense molecules induce efficient exon skipping while another antisense molecule, which targets a near-by or overlapping region, can be much less efficient. Titration studies show one compound is able to induce targeted exon skipping at 20 nM while the less efficient antisense molecules only induced exon skipping at concentrations of 300 nM and above. Therefore, we have shown that targeting of the antisense molecules to motifs involved in the splicing process plays a crucial role in the overall efficacy of that compound.

Efficacy refers to the ability to induce consistent skipping of a target exon. However, sometimes skipping of the target exons is consistently associated with a flanking exon. That is, we have found that the splicing of some exons is tightly linked. For example, in targeting exon 23 in the mouse model of muscular dystrophy with antisense molecules directed at the donor site of that exon, dystrophin transcripts missing exons 22 and 23 are frequently detected. As another example, when using an antisense molecule directed to exon 8 of the human dystrophin gene, all induced transcripts are missing both exons 8 and 9. Dystrophin transcripts missing only exon 8 are not observed.

Table 2 below discloses antisense molecule sequences that induce exon 8 (and 9) skipping.

TABLE 2

| SEQ | Antisense<br>Oligonucleotide<br>IDname | Sequence                                | Ability to induce skipping        |
|-----|--|---|-----------------------------------|
| 1   | H8A (-06+18)                           | 51-GAU AGG UGG UAU CAA<br>CAU CUG UAA   | Very strong to 20 nM              |
| 2   | H8A(-03+18)                            | 5'-GAU AGG UGG UAU CAA<br>CAU CUG       | Very strong<br>skipping to 40 nM  |
| 3   | H8A (-07+18)                           | 5'-GAU AGG UGG UAU CAA<br>CAU CUG UAA G | Strong skipping to 40 nM          |
| 4   | H8A (-06+14)                           | 5'-GGU GGU AUC AAC AUC<br>UGU AA        | Skipping to<br>300 nM             |
| 5   | H8A(-10+10)                            | 5'-GUA UCA ACA UCU GUA<br>AGC AC        | Patchy/weak<br>skipping to 100 nm |

molecule is one that induces strong and sustained exon skipping at transfection concentrations in the order of 300 nM or less.

### Antisense Oligonucleotides Directed at Exon 8

Antisense oligonucleotides directed at exon 8 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 3 shows differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. H8A(-06+18) [SEQ ID NO:1], which anneals to the last 6 bases of intron 7 and the first 18 bases of exon 8, induces substantial exon 8 and 9 skipping when delivered into cells at a concentration of 20 nM. The shorter antisense molecule, H8A(-06+14) [SEQ ID NO: 4] was only able to induce exon 8 and 9

Antisense Oligonucleotides Directed at Exon 7

Antisense oligonucleotides directed at exon 7 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 4 shows the preferred antisense molecule, H7A(+45+67) [SEQ ID NO: 6], and another antisense molecule, H7A(+2+26) [SEQ ID NO: 7], inducing exon 7 skipping. Nested amplification products span exons 3 to 9. Additional products above the induced transcript missing exon 7 arise from amplification from carry-over outer primers from the RT-PCR as well as heteroduplex formation.

Table 3 below discloses antisense molecule sequences for induced exon 7 skipping.

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TABLE :

| SEQ<br>ID | Antisense<br>Oligonucleotide<br>name | Sequen          | ce  |     |     |     |        | Ī  | Ability to induce           |
|-----------|--------------------------------------|-----------------|-----|-----|-----|-----|--------|----|-----------------------------|
| 6         | H7A(+45+67)                          | 5'-UGC<br>GG    | AUG | UUC | CAG | UCG | מעם עו | GU | Strong skipping<br>to 20 nM |
| 7         | H7A(+02+26)                          | 5'-CAC<br>CUG G | UAU | UCC | AGU | CAA | AUA G  | GU | Weak skipping at            |
| 8         | H7D(+15-10)                          | 5'-AUU<br>AGU A | UAC | CAA | ccu | UCA | GGA U  | CG | Weak skipping to            |
| 9         | H7A (-18+03)                         | 5'-GGC          | CUA | AAA | CAC | AUA | CAC A  | UA | Weak skipping to            |

Antisense Oligonucleotides Directed at Exon 6

Antisense oligonucleotides directed at exon 6 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. in human dystrophin exon 6. This compound was evaluated, found to be highly efficient at inducing skipping of that target exon, as shown in FIG. 6 and is regarded as the preferred compound for induced exon 6 skipping. Table 4 below discloses antisense molecule sequences for induced exon 6 skipping.

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TABLE 4

| SEQ II | Antisense Oligo<br>Dname | Sequence                                 | Ability to induce skipping      |
|--------|--------------------------|--|---------------------------------|
| 10     | C6A(-10+10)              | 5' CAU UUU UGA CCU ACA UGU<br>GG         | No skipping                     |
| 11     | C6A(-14+06)              | 5' UUU GAC CUA CAU GUG GAA<br>AG         | No skipping                     |
| 12     | C6A(-14+12)              | 5' UAC AUU UUU GAC CUA CAU<br>GUG GAA AG | No skipping                     |
| 13     | C6A(-13+09)              | 5' AUU UUU GAC CUA CAU GGG<br>AAA G      | No skipping                     |
| 14     | CH6A(+69+91)             | 5' UAC GAG UUG AUU GUC GGA<br>CCC AG     | Strong skipping to 20 nM        |
| 15     | C6D(+12-13)              | 5' GUG GUC UCC UUA CCU AUG<br>ACU GUG G  | Weak skipping at 300 nM         |
| 16     | C6D(+06-11)              | 5' GGU CUC CUU ACC UAU GA                | No skipping                     |
| 17     | H6D(+04-21)              | 5' UGU CUC AGU AAU CUU CUU<br>ACC UAU    | Weak skipping to 50 nM          |
| 18     | H6D(+18-04)              | 5' UCU UAC CUA UGA CUA UGG<br>AUG AGA    | Very weak skipping to<br>300 nM |

FIG. 5 shows an example of two non-preferred antisense molecules inducing very low levels of exon 6 skipping in cultured human cells. Targeting this exon for specific removal was first undertaken during a study of the canine model using the oligonucleotides as listed in Table 4, below. Some of the human specific oligonucleotides were also evaluated, as shown in FIG. 5. In this example, both antisense molecules target the donor splice site and only induced low levels of exon 6 skipping. Both H6D(+4–21) [SEQ ID NO: 17] and H6D(+18–4) [SEQ ID NO: 18] would be regarded as non-preferred antisense molecules.

One antisense oligonucleotide that induced very efficient exon 6 skipping in the canine model, C6A(+69+91) [SEQ ID NO: 14], would anneal perfectly to the corresponding region

Antisense Oligonucleotides Directed at Exon 4

Antisense oligonucleotides directed at exon 4 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 7 shows an example of a preferred antisense molecule inducing skipping of exon 4 skipping in cultured human cells. In this example, one preferred antisense compound, H4A(+13+32) [SEQ ID NO:19], which targeted a presumed exonic splicing enhancer induced efficient exon skipping at a concentration of 20 nM while other non-preferred antisense oligonucleotides failed to induce even low levels of exon 4 skipping. Another preferred antisense molecule inducing skipping of exon 4 was H4A(+1+40) [SEQ ID NO:22], which induced efficient exon skipping at a concentration of 20 nM.

Table 5 below discloses antisense molecule sequences for inducing exon 4 skipping.

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TABLE 5

|    | Antisense<br>Oligonucleotide name | Sequence                       | Ability to induce                |
|----|-----------------------------------|--------------------------------|----------------------------------|
| 19 | H4A(+13+32)                       | 5' GCA UGA ACU CUU GUG GAU CC  | skipping<br>Skipping to<br>20 nM |
| 22 | H4A(+11+40)                       |                                |                                  |
| 20 | H4D(+04-16)                       | 5' CCA CCC HAC HAS THE         | No skipping                      |
| 21 | H4D (-24-44)                      | 5' AUC GUG UGU CAC AGC AUC CAG | No skipping                      |

Antisense Oligonucleotides Directed at Exon 3

Antisense oligonucleotides directed at exon 3 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

H3A(+30+60) [SEQ ID NO:23] induced substantial exon 3 skipping when delivered into cells at a concentration of 20 nM to 600 nM. The antisense molecule, H3A(+35+65) [SEQ ID NO: 24] induced exon skipping at 300 nM.

Table 6 below discloses antisense molecule sequences that induce exon 3 skipping.

TABLE 6

| EQ : | Antisense<br>IDOligonucleotide name | Sequence                                     | Ability to<br>induce<br>skipping        |
|------|-------------------------------------|--|---|
| 23   | H3A(+30+60)                         | UAG GAG GCG CCU CCC AUC CUG UAG<br>GUC ACU G | Moderate<br>skipping to<br>20 to 600 nM |
| 24   | H3A(+35+65)                         | AGG UCU AGG AGG CGC CUC CCA UCC UGU AGG U    | Working to<br>300 nM                    |
| 25   | H3A(+30+54)                         | GCG CCU CCC AUC CUG UAG GUC ACU G            | Moderate<br>100-600 nM                  |
| 26   | H3D(+46-21)                         | CUU CGA GGA GGU CUA GGA GGC GCC<br>UC        | No skipping                             |
| 27   | H3A(+30+50)                         | CUC CCA UCC UGU AGG UCA CUG                  | Moderate 20-600 nl                      |
| 28   | H3D(+19-03)                         | UAC CAG UUU UUG CCC UGU CAG G                | No skipping                             |
| 29   | H3A(-06+20)                         | UCA AUA UGC UGC UUCCCA AAC UGA<br>AA         | No skipping                             |
| 30   | H3A(+37+61)                         | CUA GGA GGC GCC UCC CAU CCU GUA G            | No skipping                             |

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#### Antisense Oligonucleotides Directed at Exon 5

Antisense oligonucleotides directed at exon 5 were pre-pared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

H5A(+20+50) [SEQ ID NO:31] induces substantial exon 5 skipping when delivered into cells at a concentration of 100 nM. Table 7 below shows other antisense molecules tested. The majority of these antisense molecules were not as 55 effective at exon skipping as H5A(+20+50). However, H5A (+15+45) [SEQ ID NO: 40] was able to induce exon 5 skipping at 300 nM.

Table 7 below discloses antisense molecule sequences

that induce exon 5 skipping.

TABLE 7

| SEQ | Antisense<br>Oligonucleotide<br>ID name | Sequ | uence | 9   |  |     | Ability<br>induce<br>skipping |    |
|-----|---|------|-------|-----|--|-----|-------------------------------|----|
| 31  | H5A(+20+50)                             |      |       | UUU |  | ACG | Working<br>100 nM             | to |

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TABLE 7-continued

| SEQ I | Antisense<br>Oligonucleotide<br>ID name | Seq        | uenc       | Ability to<br>induce<br>skipping |            |          |     |              |
|-------|---|------------|------------|----------------------------------|------------|----------|-----|--------------|
| 32    | H5D (+25-05)                            | AUU        | ACC        | UGC                              | CAG        | UGG<br>A | AGG | No skipping  |
| 33    | H5D(+10-15)                             | CAU        | CAG        | GAU<br>G                         | ucu        | UAC      | CUG | Inconsistent |
| 34    | H5A(+10+34)                             | CGA<br>UAU | UGU<br>UCA | CAG                              | UAC        | סטכ      | CAA | Very weak    |
| 35    | H5D (-04-21)                            | ACC        | AUU        | CAU                              | CAG        | GAU      | ncn | No skipping  |
| 36    | HSD (+16-02)                            | ACC        | UGC        | CAG                              | UGG        | AGG      | AUU | No skipping  |
| 37    | H5A(-07+20)                             | CCA        | AUA        | UUC                              | ACU        | AAA      | UCA | No skipping  |
| 38    | H5D (+18-12)                            | CAG<br>GUG | GAU<br>GAG | UCU                              | UAC        | CUG      | CCA | No skipping  |
| 39    | H5A (+05+35)                            | ACG<br>AUA | AUG        | UCA<br>ACU                       | GUA<br>AAA | cuu<br>u | CCA | No skipping  |
| 40    | H5A(+15+45)                             |            |            |                                  | UAC<br>AAU |          | GUC | Working to   |

Antisense Oligonucleotides Directed at Exon 10

Antisense oligonucleotides directed at exon 10 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described

H10A(-05+16) [SEQ ID NO:41] induced substantial exon 10 skipping when delivered into cells. Table 8 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was variable. Table 8 below discloses antisense molecule sequences that induce exon 10 skipping.

TABLE 8

|    | Antisense<br>Oligonucleotide name | Seq | ienc | e    |     |     |     |       |     | lity to<br>luce skipping |
|----|-----------------------------------|-----|------|------|-----|-----|-----|-------|-----|--------------------------|
| 41 | H10A(-05+16)                      | CAG | GAG  | Gnin | CCA | AAU | GCU | GCA   | Not | tested                   |
| 42 | H10A(-05+24)                      | CUU | GUC  |      | AGG | AGC | uuc | CAA   | Not | tested                   |
| 43 | H10A(+98+119)                     | ucc | UCA  | GCA  | GAA | AGA | AGC | CAC G | Not | tested                   |
| 44 | H10A(+130+149)                    | UUA | GAA  | AUC  | UCU | CCU | UGU | GC    | No  | skipping                 |
| 45 | H10A(-33-14)                      | UAA | AUU  | GGG  | UGU | UAC | ACA | AU    | No  | skipping                 |

Antisense Oligonucleotides Directed at Exon 11

Antisense oligonucleotides directed at exon 11 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. FIG. 8B shows an example of H11A(+75+97) [SEQ ID NO:49] antisense molecule inducing exon 11 skipping in cultured human cells. H11A(+75+97) induced substantial exon 11 skipping when delivered into cells at a concentration of 5 nM. Table 9 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was observed at 100 nM.

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| SEQ | Antisense            | _          | -   | TAB | LE  | 9   | _   |     |    |                            |    |     |    |
|-----|----------------------|------------|-----|-----|-----|-----|-----|-----|----|----------------------------|----|-----|----|
| ID  | Oligonucleotide name | Sequence   |     |     |     |     |     |     |    | Ability to induce skipping |    |     |    |
| 46  | H11D(+26+49)         | CCC        | UGA | GGC | AUU | ccc | AUC | UUG |    | Skipping                   | -  | -   | _  |
| 47  | H11D(+11-09)         | AGG        | ACU | UAC | UUG | cou | UGU | טט  |    | Skipping                   | at | 100 | nM |
| 4.8 | H11A(+118+140)       | con        | GAA | טטט | AGG | AGA | uuc | AUC | UG | Skipping                   |    |     |    |
| 49  | H11A(+75+97)         | CAU        | CUU | CUG | AUA | AUU | uuc | CUG | טט | Skipping                   |    |     |    |
| 46  | H11D(+26+49)         | CCC<br>AAU | UGA | GGC | AUU | ccc | AUC | UUG |    | Skipping<br>5 nM           |    |     |    |

## Antisense Oligonucleotides Directed at Exon 12

Antisense oligonucleotides directed at exon 12 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described <sup>20</sup>

H12A(+52+75) [SEQ ID NO:50] induced substantial exon 12 skipping when delivered into cells at a concentration of 5 nM, as shown in FIG. 8A. Table 10 below shows other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The antisense molecules ability to induce exon skipping was variable.

TABLE 10

| SEQ | Antisense<br>Oligonucleotide<br>name | Seq | uenc | e   |     | Ability to<br>induce<br>skipping |
|-----|--------------------------------------|-----|------|-----|-----|----------------------------------|
| 50  | H12A(+52+75)                         | ucu | UCU  | GUU | טטט | Skipping                         |
|     |                                      | GUU | AGC  | CAG | UCA | at 5 nM                          |
| 51  | H12A(-10+10)                         | UCU | AUG  | UAA | ACU | Skipping at                      |
|     |                                      | GAA | AAU  | UU  |     | 100 nM                           |
| 52  | H12A(+11+30)                         | UUC | UGG  | AGA | UCC | No skipping                      |
|     |                                      | AUU | AAA  | AC  |     | 200 Language Cr. 2               |

#### Antisense Oligonucleotides Directed at Exon 13

Antisense oligonucleotides directed at exon 13 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H13A(+77+100) [SEQ ID NO:53] induced substantial exon 13 skipping when delivered into cells at a concentration of 5 nM. Table 11 below includes two other antisense

molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These other antisense molecules were unable to induce exon skipping.

TABLE 11

| SEQ I | Antisense<br>Oligonucleotide<br>Dname | Seq | uenc | e   |     | Ability to<br>induce<br>skipping |
|-------|---------------------------------------|-----|------|-----|-----|----------------------------------|
| 53    | H13A(+77+100)                         | CAG | CAG  | UUG | CGU | Skipping at                      |
|       |                                       | GAU | CUC  | CAC | UAG | 5 nM                             |
| 54    | H13A(+55+75)                          | uuc | AUC  | AAC | UAC | No skipping                      |
|       |                                       | CAC | CAC  | CAU |     |                                  |
| 55    | H13D(+06-19)                          | CUA | AGC  | AAA | AUA | No skipping                      |
|       |                                       | AUC | UGA  | CCU | UAA | 200                              |
|       |                                       | G   |      |     |     |                                  |

Antisense Oligonucleotides Directed at Exon 14

Antisense oligonucleotides directed at exon 14 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H14A(+37+64) [SEQ ID NO:56] induced weak exon 14 skipping when delivered into cells at a concentration of 100 nM. Table 12 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

TABLE 12

| SEQ ID | Antisense<br>Oligonucleotide<br>name | Sequence                                 | Ability to<br>induce<br>skipping |  |  |
|--------|--------------------------------------|--|----------------------------------|--|--|
| 56     | H14A(+37+64)                         | CUU GUA AAA GAA CCC AGC<br>GGU CUU CUG U | Skipping at                      |  |  |
| 57     | H14A(+14+35)                         | CAU CUA CAG AUG UUU GCC<br>CAU C         | No skipping                      |  |  |
| 58     | H14A(+51+73)                         | GAA GGA UGU CUU GUA AAA<br>GAA CC        | No skipping                      |  |  |
| 59     | H14D(-02+18)                         | ACC UGU UCU UCA GUA AGA                  | No skipping                      |  |  |

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skipping.

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TABLE 12-continued

| SEQ ID | Antisense<br>Oligonucleotide<br>name | Sequence                           | Ability to<br>induce<br>skipping |
|--------|--------------------------------------|------------------------------------|----------------------------------|
| 60     | H14D(+14-10)                         | CAU GAC ACA CCU GUU CUI<br>CAG UAA |                                  |
| 61     | H14A(+61 +80)                        | CAU UUG AGA AGG AUG UCT            | J No skipping                    |
| 62     | H14A(-12+12)                         | AUC UCC CAA UAC CUG GAG            | No skipping                      |

Antisense Oligonucleotides Directed at Exon 15

Antisense oligonucleotides directed at exon 15 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. 5 H15A(-12+19) [SEQ ID NO:63] and H15A(+48+71) [SEQ ID NO:64] induced substantial exon 15 skipping when delivered into cells at a concentration of 10 Nm, as shown in FIG. 9A. Table 13 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 Nm. These other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

TABLE 13

| SEQ I | Antisense<br>Oligonucleotide<br>Dname | Seq        | uenc     | e   |     |     |     |     |     |     | in  | ility t<br>duce<br>ipping | 0  |
|-------|---------------------------------------|------------|----------|-----|-----|-----|-----|-----|-----|-----|-----|---------------------------|----|
| 63    | H15A(-12+19)                          | GCC        | AUG<br>U | CAC | UAA | AAA | GGC | ACU | GCA | AGA | Sk: | ipping                    | at |
| 64    | H15A(+48+71)                          | UCU        | UUA      | AAG | CCA | GUU | GUG | UGA | AUC |     | 5 k | ipping<br>Jm              | at |
| 65    | H15A(+08+28)                          | מטט        | CUG      | AAA | GCC | AUG | CAC | UAA |     |     | No  | skippi                    | ng |
| 63    | H15A(-12+19)                          | GCC<br>CAU |          | CAC | UAA | AAA | GGC | ACU | GCA | AGA | No  | skippi                    | ng |
| 66    | H15D(+17-08)                          | GUA        | CAU      | ACG | GCC | AGU | טטט | UGA | AGA | C   | No  | skippi                    | nq |

Antisense Oligonucleotides Directed at Exon 16

Antisense oligonucleotides directed at exon 16 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H16A(-12+19) [SEQ ID NO:67] and H16A(-06+25) [SEQ ID NO:68] induced substantial exon 16 skipping when delivered into cells at a concentration of 10 nM, as shown in FIG. 9B. Table 14 below includes other antisense molecules tested. H16A(-06+19) [SEQ ID NO:69] and H16A(+87+109) [SEQ ID NO:70] were tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These two antisense molecules were able to induce exon skipping at 25 nM and 100 nM, respectively. Additional antisense molecules were tested at 100, 200 and 300 nM and did not result in any exon

TABLE 14

| SEQ<br>ID | Antisense<br>Oligonucleotide<br>name | Sequence                                     | Ability to<br>induce<br>skipping |
|-----------|--------------------------------------|--|----------------------------------|
| 67        | H16A(-12+19)                         | CUA GAU CCG CUU UUA AAA CCU GUU<br>AAA ACA A | Skipping at<br>5 nM              |
| 68        | H16A (-06+25)                        | UCU UUU CUA GAU CCG CUU UUA AAA<br>CCU GUU A | Skipping at<br>5 nM              |

TABLE 14-continued

| SEQ<br>ID | Antisense<br>Oligonucleotide<br>name |     | uenc | e    |      |       |       |      |      |    | in | ility to<br>duce<br>ipping |
|-----------|--------------------------------------|-----|------|------|------|-------|-------|------|------|----|----|----------------------------|
| 69        | H16A(-06+19)                         | CUA | GAU  | CCG  | cuu  | UUA   | AAA   | CCU  | GUU  | A  | sk | ipping at                  |
| 70        | H16A(+87+109)                        | CCG | UCU  | ucu  | GGG  | UCA   | CUG   | ACU  | UA   |    | sk | ipping at                  |
| 71        | H16A(-07+19)                         | CUA | GAU  | CCG  | cuu  | UUA   | AAA   | ccu  | GUU  | AA | No | skipping                   |
| 72        | H16A(-07+13)                         |     | CUU  |      |      | ccu   |       |      |      |    |    | skipping                   |
| 73        | H16A(+12+37)                         | UGG | AUU  | GCU  | טטט  | UCU   | טטט   | CUA  | GAU  | cc |    | skipping                   |
| 74        | H16A(+92+116)                        | CAU | GCU  | UCC  | GUC  |       |       |      | ACU  |    |    | skipping                   |
| 75        | H16A(+45+67)                         | G A | טכ ש | og m | JU G | AG UC | SA AU | JA C | AG U |    | No | skipping                   |
| 76        | H16A(+105+126)                       | GUU | AUC  | CAG  | CCA  | UGC   | nnc   | CGU  | c    |    | No | skipping                   |
| 77        | H16D(+05-20)                         | UGA | UAA  | UUG  | GUA  | UCA   | CUA   | ACC  | UGU  | G  |    | skipping                   |
| 78        | H16D(+12-11)                         | GUA | UCA  | CUA  | ACC  | UGU   | GCU   | GUA  | C    |    | No | skippina                   |

Antisense Oligonucleotides Directed at Exon 19

Antisense oligonucleotides directed at exon 19 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H19A(+35+65) [SEQ 1D NO:79] induced substantial exon 19 skipping when delivered into cells at a concentration of 10 nM. This antisense molecule also showed very strong exon skipping at concentrations of 25, 50, 100, 300 and 600 nM.

FIG. 10 illustrates exon 19 and 20 skipping using a "cocktail" of antisense oligonucleotides, as tested using gel electrophoresis. It is interesting to note that it was not easy to induce exon 20 skipping using single antisense oligonucleotides H20A(+44+71) [SEQ ID NO:81] or H20A(+40+149+170) [SEQ ID NO:82], as illustrated in sections 2 and 3 of the gel shown in FIG. 10. Whereas, a "cocktail" of antisense oligonucleotides was more efficient as can be seen in section 4 of FIG. 10 using a "cocktail" of antisense oligonucleotides H20A(+44+71) and H20A(+149+170). 45 When the cocktail was used to target exon 19, skipping was even stronger (see section 5, FIG. 10).

FIG. 11 illustrates gel electrophoresis results of exon 19/20 skipping using "weasels" The "weasels" were effec-

25 tive in skipping exons 19 and 20 at concentrations of 25, 50, 100, 300 and 600 nM. A further "weasel" sequence is shown in the last row of Table 3C. This compound should give good results.

Antisense Oligonucleotides Directed at Exon 20

Antisense oligonucleotides directed at exon 20 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

None of the antisense oligonucleotides tested induced exon 20 skipping when delivered into cells at a concentration of 10, 25, 50, 300 or 600 nM (see Table 15). Antisense molecules H20A(-11+17) [SEQ ID NO:86] and H20D(+08-20) [SEQ ID NO:87] are yet to be tested.

However, a combination or "cocktail" of H20A(+44+71) [SEQ ID NO: 81] and H20(+149+170) [SEQ ID NO:82] in a ratio of 1:1, exhibited very strong exon skipping at a concentration of 100 nM and 600 nM. Further, a combination of antisense molecules H19A(+35+65) [SEQ ID NO:79], H20A(+44+71) [SEQ ID NO:81] and H20A(+149+170) [SEQ ID NO:82] in a ratio of 2:1:1, induced very strong exon skipping at a concentration ranging from 10 nM to 600 nM.

TABLE 15

| SEQ | Antisense<br>Oligonucleotide<br>name | Sequence                                 | Ability to<br>induce<br>skipping |
|-----|--------------------------------------|--|----------------------------------|
| 81  | H20A(+44+71)                         | CUG GCA GAA UUC GAU CCA CCG GCU<br>GUU C | No<br>skipping                   |
| 82  | H20A(+147+168)                       | CAG CAG UAG UUG UCA UCU GCU C            | No<br>skipping                   |
| 83  | H20A(+185+203)                       | UGA UGG GGU GGU GGG UUG G                | No<br>skipping                   |
| 84  | H20A (-08+17)                        | AUC UGC AUU AAC ACC CUC UAG AAA G        | No<br>skipping                   |

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TABLE 15-continued

| SEQ            | Antisense<br>Oligonucleotide<br>name | Sequence                                      | Ability to<br>induce<br>skipping |
|----------------|--------------------------------------|---|----------------------------------|
| 85             | H20A(+30+53)                         | CCG GCU GUU CAG UUG UUC UGA GGC               | No<br>skipping                   |
| 86             | H20A(-11+17)                         | AUC UGC AUU AAC ACC CUC UAG AAA GAA A         | Not tested<br>yet                |
| 87             | H20D(+08-20)                         | GAA GGA GAA GAG AUU CUU ACC UUA<br>CAA A      | Not tested<br>yet                |
| 81 &<br>82     | H20A(+44+71) &<br>H20A(+147+168)     | CUG GCA GAA UUC GAU CCA CCG GCU               | Very strong                      |
|                |                                      | CAG CAG UAG UUG UCA UCU GCU C                 | skipping                         |
| 80, 81<br>& 82 | H19A(+35+65);<br>H20A(+44+71);       | GCC UGA GCU GAU CUG CUG GCA UCU<br>UGC AGU U; | Very strong                      |
|                | H20A(+147+168)                       | CUG GCA GAA UUC GAU CCA CCG GCU               | pribbing                         |
|                |                                      | CAG CAG UAG UUG UCA UCU GCU C                 |                                  |

Antisense Oligonucleotides Directed at Exon 21

Antisense oligonucleotides directed at exon 21 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H21A(+85+108) [SEQ ID NO:92] and H21A(+85+106) [SEQ ID NO:91] induced exon 21 skipping when delivered into cells at a concentration of 50 nM. Table 16 below includes other antisense molecules tested at a concentration 35 range of 5, 25, 50, 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping

TABLE 16

|    | Antisense<br>Oligonucleotide name |            |      |     |     |     |     |     |   | Ability to induce skipping |     |         |  |
|----|-----------------------------------|------------|------|-----|-----|-----|-----|-----|---|----------------------------|-----|---------|--|
| 90 | H21A(-06+16)                      | GCC        | GGU  | UGA | CUU | CAU | CCU | GUG | C | Skips                      | at  | 600 nM  |  |
| 91 | H21A(+85+106)                     | CUG        | CAU  | CCA | GGA | ACA | UGG | GUC | C | Skips                      | at  | 50 nM   |  |
| 92 | H21A(+85+108)                     | GUC        | UGC  | AUC | CAG | GAA | CAU | GGG |   | Skips                      | at  | 50 nM   |  |
| 93 | H21A(+08+31)                      | GUU<br>UGA | GAA  | GAU | CUG | AUA | GCC | GGU |   | Skips                      | fai | ntly to |  |
| 94 | H21D(+18-07)                      | UAC        | UUA. | cug | บตบ | GUA | GCU | can |   | No ski                     | ppi | ng      |  |

Antisense Oligonucleotides Directed at Exon 22

Antisense oligonucleotides directed at exon 22 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 12 illustrates differing efficiencies of two antisense molecules directed at exon 22 acceptor splice site. H22A(+

55 125+106) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO: 98] induce strong exon 22 skipping from 50 nM to 600 nM concentration.

H122A(+125+146) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO:98] induced exon 22 skipping when delivered into cells at a concentration of 50 nM. Table 17 below shows other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed a variable ability to induce exon skipping.

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TABLE 17

| SEQ I | Antisense<br>oligonucleotide<br>D name | Seq        | uenc | e   |     |     |     |       | Ability to induce  |
|-------|--|------------|------|-----|-----|-----|-----|-------|--------------------|
| 95    | H22A(+22+45)                           | CAC<br>GCA | UCA  | UGG | aca | ccu | GAU | AGC   | No skipping        |
| 96    | H22A(+125+146)                         | CUG        | CAA  | UUC | ccc | GAG | ucu | CUG C | Skipping to 50 nM  |
| 97    | H22A(+47+69)                           | ACU<br>UG  | GCU  | GGA | ccc | AUG | ucc | UGA   | Skipping to 300 nM |
| 98    | H22A(+B0+101)                          | CUA        | AGU  | UGA | GGU | AUG | GAG | AGU   | Skipping to 50 nM  |
| 99    | H22D(+13-11)                           | UAU        | UCA  | CAG | ACC | UGC | AAU | ПСС   | No skipping        |

Antisense Oligonucleotides Directed at Exon 23

Antisense oligonucleotides directed at exon 23 were pre- 20 skipping, pared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 18 below shows antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These 2 antisense molecules showed no ability to induce exon skipping or are yet to be tested.

TABLE 18

| SEQ II | Antisense<br>oligonucleotide<br>Dname | Seq | uenc       | e |     | in | ility to<br>duce<br>ipping |
|--------|---------------------------------------|-----|------------|---|-----|----|----------------------------|
| 100    | H23A(+34+59)                          |     | GUG<br>UAG |   |     | No | skipping                   |
| 101    | H23A(+18+39)                          |     | GCC        |   |     | No | Skipping                   |
| 102    | H23A(+72+90)                          |     | AGA<br>CUU |   | CGC | No | Skipping                   |

#### Antisense Oligonucleotides Directed at Exon 24

Antisense oligonucleotides directed at exon 24 were prepared using similar methods as described above. Table 19 below outlines the antisense oligonucleotides directed at exon 24 that are yet to be tested for their ability to induce exon 24 skipping.

TABLE 19

|     | Antisense<br>oligonucleotide<br>name | Seq        | uenc | e          |           | Abili<br>induce<br>skipp | e       | 55 |
|-----|--------------------------------------|------------|------|------------|-----------|--------------------------|---------|----|
| 103 | H24A(+48+70)                         | GGG        | CAG  | GCC<br>UCA | AUU<br>GA | Needs                    | testing |    |
| 104 | H24A(-02+22)                         | UCU<br>GUA | UCA  | GGG<br>GAU | מכט       | Needs                    | testing | 60 |

# Antisense Oligonucleotides Directed at Exon 25

Antisense oligonucleotides directed at exon 25 were prepared using similar methods as described above. Table 20 50

below shows the antisense oligonucleotides directed at exon 25 that are yet to be tested for their ability to induce exon 25 skipping.

TABLE 20

| SEQ<br>ID | Antisense<br>oligonucleotide<br>name | Seque                   | nce | ė | Ability to<br>induce<br>skipping |       |         |
|-----------|--------------------------------------|-------------------------|-----|---|----------------------------------|-------|---------|
| 105       | H25A(+9+36)                          | GUG GO<br>GUC UCA<br>CI | 3A  |   | AUU                              | Needs | testing |
| 106       | H25A(+131+156)                       | CUG UI<br>GUG AU<br>AG  |     |   |                                  | Needs | testing |
| 107       | H25D(+16-08)                         | GUC U                   |     |   |                                  | Needs | testing |

#### Antisense Oligonucleotides Directed at Exon 26

Antisense oligonucleotides directed at exon 26 were prepared using similar methods as described above. Table 21 below outlines the antisense oligonucleotides directed at exon 26 that are yet to be tested for their ability to induce exon 26 skipping.

TABLE 21

| SEQ | Antisense<br>oligonucleotide<br>name | Seq             | uenc | e   | Ability to<br>induce<br>skipping |                           |         |
|-----|--------------------------------------|-----------------|------|-----|----------------------------------|---------------------------|---------|
| 108 | H26A(+132+156)                       |                 |      | CUG |                                  | Needs                     | testing |
| 109 | H26A(-07+19)                         |                 |      | CCA |                                  | Needs                     | testing |
| 110 | H26A(+68+92)                         | UGU<br>UCG<br>G |      | AUC | CAU                              | Faint<br>skippi<br>at 600 | -       |

#### Antisense Oligonucleotides Directed at Exon 27

Antisense oligonucleotides directed at exon 27 were prepared using similar methods as described above. Table 22 below outlines the antisense oligonucleotides directed at exon 27 that are yet to be tested for their ability to induce exon 27 skipping.

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TABLE 22

| SEQ I | Antisense<br>oligonucleotide<br>Dname | Seq        | uenc     | e   |     |     |     |     | Ability to induce |
|-------|---------------------------------------|------------|----------|-----|-----|-----|-----|-----|-------------------|
| 111   | H27A(+82+106)                         | UUA<br>GUG | AGG<br>G | ccu | cuu | GUG | CUA | CAG |                   |
| 112   | H27A(-4+19)                           | GGG<br>GA  | ccu      | CUU | cuu | UAG | cuc | טכט | Faint skipping at |
| 112   | H27D(+19-03)                          | GAC        | UUC      | CAA | AGU | cuu | GCA | טטט |                   |

Antisense Oligonucleotides Directed at Exon 28

Antisense oligonucleotides directed at exon 28 were prepared using similar methods as described above. Table 23 below outlines the antisense oligonucleotides directed at exon 28 that are yet to be tested for their ability to induce 20 exon 28 skipping.

TABLE 23

| SEQ I | Antisense<br>oligonucleotide<br>Dname | Seq        | uenc | e   |     |     |     |     | Ability to induce skipping              |
|-------|---------------------------------------|------------|------|-----|-----|-----|-----|-----|---|
| 114   | H28A(-05+19)                          | GCC<br>AAG | AAC  | AUG | ccc | AAA | COU | CCU | v. strong skipping<br>at 600 and 300 nM |
| 115   | H28A(+99+124)                         | CAG<br>CAG |      | טטט | ccu | CAG | COC | CGC | Needs testing                           |
| 116   | H28D(+16-05)                          | COO        | ACA  | ncn | AGC | ACC | UCA | GAG | v. strong skipping<br>at 600 and 300 nM |

Antisense Oligonucleotides Directed at Exon 29

Antisense oligonucleotides directed at exon 29 were prepared using similar methods as described above. Table 24 40 below outlines the antisense oligonucleotides directed at exon 29 that are yet to be tested for their ability to induce exon 29 skipping.

TABLE 24

| SEQ I | Antisense<br>oligonucleotide<br>Dname | Seq | ienc     | e   |     |     |     |     |   |          | ility to induce                   |
|-------|---------------------------------------|-----|----------|-----|-----|-----|-----|-----|---|----------|-----------------------------------|
| 117   | H29A(+57+81)                          | UCC | GCC<br>C | AUC | UGU | UAG | GGU | CUG |   | Ne       | eds testing                       |
| 118   | H29A(+18+42)                          | AUU | UGG<br>C | GUU | AUC | CUC | UGA | AUG |   | v.<br>at | strong skipping<br>600 and 300 nM |
| 119   | H29D(+17-05)                          | CAU | ACC      | ucu | UCA | UGU | AGU | UCC | c |          | strong skipping<br>600 and 300 nM |

Antisense Oligonucleotides Directed at Exon 30

Antisense oligonucleotides directed at exon 30 were prepared using similar methods as described above. Table 25 below outlines the antisense oligonucleotides directed at exon 30 that are yet to be tested for their ability to induce exon 30 skipping.

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TABLE 25

| SEQ I | Antisense<br>oligonucleotide<br>Dname | Seq        | uenc       | e         |     |     |     | Ability to induce skipping                 |
|-------|---------------------------------------|------------|------------|-----------|-----|-----|-----|--|
| 120   | H30A(+122+147)                        | CAU        | UUG<br>GUC | AGC<br>UG | UGC | GUC | CAC |  |
| 121   | H30A(+25+50)                          | CUC        | UGG        | GCA<br>UC | GAC | UGG | AUG | Very strong skipping at<br>600 and 300 nM. |
| 122   | H30D(+19-04)                          | DUG<br>GCA | CCU        | GGG       | CUU | ccu | GAG | Very strong skipping at<br>600 and 300 nM. |

Antisense Oligonucleotides Directed at Exon 31

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Antisense oligonucleotides directed at exon 31 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 13 illustrates differing efficiencies of two antisense molecules directed at exon 31 acceptor splice site and a "cocktail" of exon 31 antisense oligonucleotides at varying concentrations. H31D(+03-22) [SEQ ID NO:124] substantially induced exon 31 skipping when delivered into cells at a concentration of 20 nM. Table 26 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

#### TABLE 26

| SEQ I | Antisense<br>oligonucleotide<br>D name | Seq        | uenc     | e   |     |     |     |     | Ability to induce skipping |  |  |
|-------|--|------------|----------|-----|-----|-----|-----|-----|----------------------------|--|--|
| 123   | H31D(+06-18)                           | UUC        | UGA      | AAU | AAC | AUA | UAC | CUG | Skipping to 300 n          |  |  |
| 124   | H31D(+03-22)                           | UAG<br>CCU | UUU<br>G | CUG | AAA | UAA | CAU | ÁUA | Skipping to 20 nM          |  |  |
| 125   | H31A(+05+25)                           | GAC        | UUG      | UCA | AAU | CAG | AUU | GGA | No skipping                |  |  |
| 126   | H31D(+04-20)                           | GUU        | ucu      | GAA | AUA | ACA | UAU | ACC | Skipping to 300 n          |  |  |

### Antisense Oligonucleotides Directed at Exon 32

Antisense oligonucleotides directed at exon 32 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. 5 H32D(+04-16) [SEQ ID NO:127] and H32A(+49+73) [SEQ ID NO:130] induced exon 32 skipping when delivered into cells at a concentration of 300 nM. Table 27 below also shows other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules did not show an ability to induce exon skipping.

#### TABLE 27

| SEQ<br>ID | Antisense<br>oligonucleotide<br>name | Seq       | tenc     | e   |     |     |     |     | Abili | -   | to : | indu | ce |
|-----------|--------------------------------------|-----------|----------|-----|-----|-----|-----|-----|-------|-----|------|------|----|
| 127       | H32D(+04-16)                         | CAC       | CAG      | AAA | UAC | AUA | CCA | CA  | Skipp | ing | to   | 300  | nM |
| 128       | H32A(+151+170)                       | CAA       | UGA      | מטמ | AGC | UGU | GAC | UG  | No sk | ipp | ing  |      |    |
| 129       | H32A(+10+32)                         | CGA<br>UG | AAC      | uuc | AUG | GAG | ACA | ucu | No sk | ipp | ing  |      |    |
| 130       | H32A(+49+73)                         | CUU       | GUA<br>C | GAC | GCU | GCU | CAA | AAU | Skipp | ing | to   | 300  | nM |

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Antisense Oligonucleotides Directed at Exon 33

Antisense oligonucleotides directed at exon 33 were prepared and tested for their ability to induce exon skipping in 5 human muscle cells using similar methods as described above. 56

FIG. 14 shows differing efficiencies of two antisense molecules directed at exon 33 acceptor splice site. H33A(+64+88) [SEQ ID NO:134] substantially induced exon 33 skipping when delivered into cells at a concentration of 10 nM. Table 28 below includes other antisense molecules tested at a concentration of 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 28

| SEQ I | Antisense<br>oligonucleotide<br>D name |            | uenc | e   |     |     |     |     |       | Ability to induce skipping |
|-------|--|------------|------|-----|-----|-----|-----|-----|-------|----------------------------|
| 131   | H33D(+09-11)                           | CAU        | GCA  | CAC | ACC | טטט | GCU | cc  |       | No skipping                |
| 132   | H33A (+53+76)                          | טכט        | GUA  | CAA | ucu | GAC | GUC | CAG | ucu   | Skipping to 200 nM         |
| 133   | H33A(+30+56)                           | GUG<br>GAC | טטט  | AUC | ACC | AUU | ucc | ACU | UCA   | Skipping to 200 nM         |
| 134   | H33A (+64+88)                          | GCG        | UCU  | GCU | טטט | ucu | GUA | CAA | UCU G | Skipping to 10 nM          |

Antisense Oligonucleotides Directed at Exon 34

25 Antisense oligonucleotides directed at exon 34 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 29 below includes antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 29

| SEQ ID | Antisense<br>oligonucleotide<br>name | Seq        | uenc       | e          |     |     |     | Ability to induce skipping |
|--------|--------------------------------------|------------|------------|------------|-----|-----|-----|----------------------------|
| 135    | H34A(+83+104)                        | UCC<br>AGC |            | ncn        | GUA | GCU | GGC | No skipping                |
| 136    | H34A(+143+165)                       | CCA        |            | AAC        | UUC | AGA | AUC | No skipping                |
| 137    | H34A(-20+10)                         | UUU<br>AAU |            | UUA<br>AAU |     | GAA | AAG | Not tested                 |
| 138    | H34A(+46+70)                         | CAU        | UCA        |            | CCU | UUC | GCA | Skipping to 300 nM         |
| 139    | H34A(+95+120)                        | 7. 3       | UCU        | CUU<br>UG  | UGU | CAA | uuc | Skipping to 300 nM         |
| 140    | H34D(+10-20)                         |            |            | GAU        |     | GGU | טטט | Not tested                 |
| 141    | H34A(+72+96)                         | CUG        | UAG<br>UCA |            | CCA | GCC | AUU | No skipping                |

55 Antisense Oligonucleotides Directed at Exon 35

Antisense oligonucleotides directed at exon 35 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 15 shows differing efficiencies of antisense molecules directed at exon 35 acceptor splice site. H35A(+24+43) [SEQ ID NO:144] substantially induced exon 35 skipping when delivered into cells at a concentration of 20 nM. Table 30 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed no ability to induce exon skipping.

ð ....

TABLE 30

| SEQ I | Antisense<br>oligonucleotide<br>Dname |     | uenc | e   |     |     |     |     | Ability to induce |
|-------|---------------------------------------|-----|------|-----|-----|-----|-----|-----|-------------------|
| 142   | H35A(+141+161)                        | UCU | ucu  | GCU | CGG | GAG | GUG | ACA | skipping to 20 nM |
| 143   | H35A(+116+135)                        | CCA |      |     |     |     |     |     | No skipping       |
| 144   | H35A(+24+43)                          | UCU | UCA  | GGU | GCA | CCU | UCU | GU  | No skipping       |

Antisense Oligonucleotides Directed at Exon 36

Antisense oligonucleotides directed at exon 36 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense molecule H36A(+26+50) [SEQ ID NO:145] <sup>20</sup> induced exon 36 skipping when delivered into cells at a concentration of 300 nM, as shown in FIG. 16.

Antisense Oligonucleotides Directed at Exon 37

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Antisense oligonucleotides directed at exon 37 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 17 shows differing efficiencies of two antisense molecules directed at exon 37 acceptor splice site. H37A(+82+105) [SEQ ID NO:148] and H37A(+134+157) [SEQ ID NO:149] substantially induced exon 37 skipping when delivered into cells at a concentration of 10 nM. Table 31 below shows the antisense molecules tested.

TABLE 31

| SEQ I | Antisense<br>oligonucleotide<br>D name | Seq | ienc | е   |     |     |     |     |       | Ability to skipping | induce |
|-------|--|-----|------|-----|-----|-----|-----|-----|-------|---------------------|--------|
| 147   | H37A (+26+50)                          | CGU | GUA  | GAG | UCC | ACC | טטט | GGG | CGU A | No skipping         |        |
| 148   | H37A(+82+105)                          | UAC | UAA  | טטט | ccu | GCA | GUG | GUC | ACC   | Skipping to         | 10 nM  |
| 149   | H37A(+134+157)                         | uuc | UGU  | GUG | AAA | UGG | cug | CAA | AUC   | Skipping to         | 10 nM  |

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Antisense Oligonucleotides Directed at Exon 38

Antisense oligonucleotides directed at exon 38 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 18 illustrates antisense molecule H38A(+88+112)
 [SEQ ID NO:152], directed at exon 38 acceptor splice site.
 H38A(+88+112) substantially induced exon 38 skipping when delivered into cells at a concentration of 10 nM. Table 32 below shows the antisense molecules tested and their ability to induce exon skipping.

TABLE 32

| SEQ | Antisense<br>oligonucleotide<br>name | Sequ       | ience    | 2   |     |     |     |     | Ability<br>skipping | to  | ind | uce |
|-----|--------------------------------------|------------|----------|-----|-----|-----|-----|-----|---------------------|-----|-----|-----|
| 150 | H38A(-01+19)                         | CCU        | ŲCA      | AAG | GAA | UGG | AGG | cc  | No skipp            | ing | ,   |     |
| 151 | H38A (+59+83)                        | UGC        |          | AUU | UCA | GCC | UCC | AGU | Skipping            | to  | 10  | nM  |
| 152 | H38A(+88+112)                        | UGA<br>UCA | AGU<br>C | cuu | ccu | cuu | UCA | GAU | Skipping            | to  | 10  | nM  |

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Antisense Oligonucleotides Directed at Exon 39

Antisense oligonucleotides directed at exon 39 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above. H39A(+62+85) [SEQ ID NO:153] induced exon 39 skipping when delivered into cells at a concentration of 100 nM. Table 33 below shows the antisense molecules tested and their ability to induce exon skipping.

TABLE 33

| SEQ I | Antisense<br>oligonucleotide<br>Dname | Seq | uenc | 9   |     |     |     |     | Ability to induce skipping |
|-------|---------------------------------------|-----|------|-----|-----|-----|-----|-----|----------------------------|
| 153   | H39A (+62+85)                         | CUG | GCU  | uuc | UCU | CAU | CUG | UGA | Skipping to 100 nM         |
| 154   | H39A(+39+58)                          | GUU | GUA  | AGU | UGU | CUC | CUC | υu  | No skipping                |
| 155   | H39A(+102+121)                        | UUG | UCU  | GUA | ACA | GCU | GCU | GU  | No skipping                |
| 156   | H39D(+10-10)                          | GCU | CUA  | AUA | CCU | UGA | GAG | CA  | Skipping to 300 nM         |

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Antisense Oligonucleotides Directed at Exon 40

Antisense oligonucleotides directed at exon 40 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 19 illustrates antisense molecule H40A(-05+17) [SEQ ID NO:157] directed at exon 40 acceptor splice site. H40A(-05+17) and H40A(+129+153) [SEQ ID NO:158] both substantially induced exon 40 skipping when delivered into cells at a concentration of 5 nM.

Antisense Oligonucleotides Directed at Exon 42

Antisense oligomucleotides directed at exon 42 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 20 illustrates antisense molecule H42A(-04+23) [SEQ ID NO:159], directed at exon 42 acceptor splice site, H42A(-4+23) and H42D(+19-02) [SEQ ID NO:161] both induced exon 42 skipping when delivered into cells at a concentration of 5 nM. Table 34 below shows the antisense molecules tested and their ability to induce exon 42 skipping.

TABLE 34

| SEQ I | Antisense<br>afigonucleotide<br>Dname | Sequence                               | Ability to induce skipping |  |  |
|-------|---------------------------------------|--|----------------------------|--|--|
| 159   | H42A(-4+23)                           | AUC GUU UCU UCA CGG ACA GUG<br>UGG UGC | Skipping to 5 nM           |  |  |
| 160   | H42A(+86+109)                         | GGG COU GUG AGA CAU GAG UGA            | Skipping to 100 nM         |  |  |
| 161   | H42D(+19-02)                          | A CCU UCA GAG GAC UCC UCU<br>UGC       | Skipping to 5 nM           |  |  |

#### Antisense Oligonucleotides Directed at Exon 43

- Antisense oligonucleotides directed at exon 43 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.
- H43A(+101+120) [SEQ ID NO:163] induced exon 43
  65 skipping when delivered into cells at a concentration of 25
  nM. Table 35 below includes the antisense molecules tested
  and their ability to induce exon 43 skipping.

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TABLE 35

| SEQ I | Antisense<br>oligonucleotide<br>D name | Seq | uenc     | e   |     |     | Ability to induce |        |                    |
|-------|--|-----|----------|-----|-----|-----|-------------------|--------|--------------------|
| 162   | H43D(+10-15)                           | UAU | GUG<br>C | UUA | CCU | ACC | cuu               | GUC    | Skipping to 100 nM |
| 163   | H43A(+101+120)                         | GGA | GAG      | AGC | UUC | CUG | UAG               | cu     | Skipping to 25 nM  |
| 164   | H43A(+78+100)                          | UCA | ccc      | טטט | CCA | CAG | GCG               | UUG CA | Skipping to 200 nM |

Antisense Oligonucleotides Directed at Exon 44

Antisense oligonucleotides directed at exon 44 were prepared using similar methods as described above. Testing for the ability of these antisense molecules to induce exon 44 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 165 to 167 in Table 1A.

Antisense Oligonucleotides Directed at Exon 45

Antisense oligonucleotides directed at exon 45 were prepared using similar methods as described above. Testing for the ability of these antisense molecules to induce exon 45 25 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 207 to 211 in Table 1A.

Antisense Oligonucleotides Directed at Exon 46

Antisense oligonucleotides directed at exon 46 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 21 illustrates the efficiency of one antisense molceule directed at exon 46 acceptor splice site. Antisense oligonucleotide H46A(+86+115) [SEQ ID NO:203] showed very strong ability to induce exon 46 skipping. Table 36 below includes antisense molecules tested. These antisense molecules showed varying ability to induce exon 46 skipping.

H47A(+76+100) [SEQ ID NO:170] and H47A(-09+12) [SEQ ID NO:172] both induced exon 47 skipping when delivered into cells at a concentration of 200 nM. H47D(+25-02) [SEQ ID NO: 171] is yet to be prepared and tested.

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Antisense Oligonucleotides Directed at Exon 50

Antisense oligonucleotides directed at exon 50 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense oligonucleotide molecule H50A(+02+30) [SEQ ID NO: 173] was a strong inducer of exon skipping. Further, H50A(+07+33) [SEQ ID NO:174] and H50D(+07-18) [SEQ ID NO:175] both induced exon 50 skipping when delivered into cells at a concentration of 100 nM.

Antisense Oligonucleotides Directed at Exon 51

Antisense oligonucleotides directed at exon 51 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 22 illustrates differing efficiencies of two antisense molecules directed at exon 51 acceptor splice site. Antisense oligonucleotide H51A(+66+90) [SEQ ID NO:180] showed the stronger ability to induce exon 51 skipping. Table 37

TABLE 36

| SEQ II | Antisense<br>oligonucleotide<br>Dname | Seq        | uenc       | Ability to<br>induce<br>skipping |     |     |     |     |     |      |                   |
|--------|---------------------------------------|------------|------------|----------------------------------|-----|-----|-----|-----|-----|------|-------------------|
| 168    | H46D(+16-04)                          | UUA        | CCU        | UGA                              | cuu | GCU | CAA | GC  | -   | No s | kipping           |
| 169    | H46A(+90+109)                         | ucc        | AGG        | UUC                              | AAG | UGG | GAU | AC  |     | No s | kipping           |
| 203    | H46A(+86+115)                         | CUC        | UUU<br>AGC | ncc                              | AGG | uuc | AAG | UGG | GAU |      | skipping<br>00 nM |
| 204    | H46A(+107+137)                        | CAA        | GCU        |                                  | CUU | UUA | GUU | GCU | GCU |      | skipping<br>00 nM |
| 205    | H46A(-10+20)                          | UAU<br>AGA | UCU<br>AAG | טטט                              | GUU | can | CUA | GCC | UGG | Weak | skipping          |
| 206    | H46A(+50+77)                          | 77.2.0     | cuu        | ccu                              | CCA | ACC | AUA | AAA | CAA | Weak | skipping          |

Antisense Oligonucleotides Directed at Exon 47

Antisense oligonucleotides directed at exon 47 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

below includes antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 51 skipping. The strongest inducers of exon skipping were antisense oligonucleotide H51A(+61+90) [SEQ ID NO: 179] and H51A(+66+95) [SEQ ID NO: 181].

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TABLE 37

| Antisense<br>oligonucleotide<br>SEQ ID name |                             |                   | uenc       | e          |            | Alt        | Ability to induce skipping |                     |
|---|-----------------------------|-------------------|------------|------------|------------|------------|----------------------------|---------------------|
| 176   | H51A(-01+25)                | ACC<br>UGA        | AGA<br>GUA | GUA        | ACA<br>GC  | GUC        |                            | int skipping        |
| 177   | H51D(+16-07)                | CUC               | AUA<br>UGA | CCU        | ncn        | GCU        | Sk                         | ipping at 300 nM    |
| 178   | H51A(+111+134)              | UUC               | UGU        | CCA        | AGC        | ccc        | Ne                         | eds re-testing      |
| 179   | H51A(+61+90)                | ACA<br>GCA        | UCA        | AGG<br>CUA | AAG        | AUG        | Ve                         | ry strong           |
| 180   |                             |                   | UCA        | AGG        | AAG        |            |                            | ipping              |
| 181   | H51A(+66+95)                | CUC<br>AGA        | CAA        | CAU        | CAA        | GGA<br>UAG | Ve                         | ry strong<br>ipping |
| 192   | H51D(+08-17)                | AUC<br>ACC        | AUU        | UUU        | ucu<br>u   | CAU        | No                         | skipping            |
| 183   | H51A/D(+08-17)<br>& (-15+?) | AUC<br>ACC<br>CUA | OOC        | UGC        | UCU<br>UAG | CAU        | No                         | skipping            |
| 184   | H51A(+175+195)              | CAC               | CCA<br>GUG | CCA        | UCA        | GCC        | No                         | skipping            |
| 185   | H51A(+199+220)              | AUC               | AUC        | UCG<br>A   | UUG        | AUA        | No                         | skipping            |

Antisense Oligonucleotides Directed at Exon 52

Antisense oligonucleotides directed at exon 52 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 22 also shows differing efficiencies of four antisense 40 molecules directed at exon 52 acceptor splice site. The most effective antisense oligonucleotide for inducing exon 52 skipping was H52A(+17+37) [SEQ ID NO:188).

Table 38 below shows antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 50 skipping. Antisense molecules H52A(+12+41) [SEQ ID NO:187] and H52A(+17+37) [SEQ ID NO:188] showed the strongest exon 50 skipping at a concentration of 50 nM.

Antisense Oligonucleotides Directed at Exon 53

Antisense oligonucleotides directed at exon 53 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 22 also shows antisense molecule H53A(+39+69) [SEQ ID NO:193] directed at exon 53 acceptor splice site. This antisense oligonucleotide was able to induce exon 53 skipping at 5, 100, 300 and 600 nM. A "cocktail" of three exon 53 antisense oligonucleotides: H53A(+23+47) [SEQ ID NO:195], H53A(+150+176) [SEQ ID NO:196] and H53D(+14-07) [SEQ ID NO:194], was also tested, as shown in FIG. 20 and exhibited an ability to induce exon skipping.

Table 39 below includes other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 53 skipping. Antisense molecule H53A(+39+69) [SEQ ID NO:193] induced the strongest exon 53 skipping.

TABLE 38

|     | Antisense<br>oligonucleotide<br>name | Seq | uenc | e   |     |     |     |        | Ability to induce skipping |
|-----|--------------------------------------|-----|------|-----|-----|-----|-----|--------|----------------------------|
| 186 | H52A(-07+14)                         | UCC | UGC  | AUU | GUU | GCC | UGU | AAG    | No akipping                |
| 187 | H52A(+12+41)                         |     | AAC  |     | GGA | CGC | cuc | ugu ud | C Very strong<br>skipping  |
| 188 | H52A(+17+37)                         | ACU | GGG  | GAC | GCC | UCU | GUU | CCA    | Skipping to<br>50 nM       |
| 189 | H52A(+93+112)                        | CCG | UAA  | UGA | UUG | nnc | DAG | CC     | No skipping                |
| 190 | H52D(+05-15)                         | UGU | UAA  | AAA | ACU | UAC | UUC | GA     | No skipping                |

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201 H53A(+07+26)

202 H53A(+124+145)

AAG A

| _                |  |            | T          | ABLI       | 39       | )                 |                   |                                 |
|------------------|--|------------|------------|------------|----------|-------------------|-------------------|---------------------------------|
| SEQ I            | Antisense<br>oligonucleotide<br>D name |            | uenc       | e          |          | Ability to induce |                   |                                 |
| 191 H53A(+45+69) | CAU                                    | UCA        | ACU<br>G   | GUU        | GCC      | ucc               | Faint skipping at |                                 |
| 192              | H53A(+39+62)                           | CUG        | UUG        | ccu        | CCG      | GUU               | cug               |                                 |
| 193              | H53A(+39+69)                           | CAU        | UCA        | ACU        | GUU      | GCC               | UCC               | Strong skipping<br>to 50 nM     |
| 194              | H53D(+14-07)                           | UAC        | UAA        | CCU        | UGG      | טטט               | CUG               | Very faint<br>skipping to 50 nM |
| 195              | H53A(+23+47)                           | CUG        | AAG<br>UUC | GUG<br>AUC | onc<br>c | UUG               |                   | Very faint<br>skipping to 50 nM |
| 196              | H53A(+150+176)                         | UGU        | AUA<br>UGA | GGG        | ACC      | CUC               | CUU               |                                 |
| 197              | H53D (+20-05)                          | CUA        | ACC<br>UUC | UUG<br>U   | GUU      | ucu               | GUG               |                                 |
| 198              | H53D(+09-18)                           |            | AUC        |            |          | ACU               |                   | Faint at 600 nM                 |
| 199              | H53A(-12+10)                           |            | CUU        |            | ACU      | AGA               |                   | No skipping                     |
| 200              | H53A(-07+18)                           | GAU<br>CAA | UCU        |            |          | טטט               |                   | No skipping                     |
|                  |  |            |            |            |          |                   |                   |                                 |

#### SEQUENCE LISTING

AUC CCA CUG AUU CUG AAU No skipping

UUG GCU CUG GCC UGU CCU No skipping

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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Human 2'-O-methyl phosphorothicate antisense

oligonucleotide

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79
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81

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1220 > FEATURE:

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83

cageaguuge gugaueueea euag

-continued c223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothioate antisense <400> SEQUENCE: 48 cuugaauuua ggagauucau cug 23 <210> SEQ ID NO 49 <211> LENGTH: 23 <212> TYPE: RNA <213 > ORGANISM: Artificial Sequence <220> FEATURE: 223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothicate antisense <400> SEQUENCE: 49 caucuucuga uaauuuuccu guu 23 <210> SEQ ID NO 50 <211> LENGTH: 24 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothicate antisense oligonucleotide 400> SEQUENCE: 50 ucuucuguuu uuguuagcca guca 24 <210> SEQ ID NO 51 <211> LENGTH: 20 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 51 20 ucuauguaaa cugaaaauuu <210> SEQ ID NO 52 <211> LENGTH: 20 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 52 20 ичсиддадам ссациалаас <210> SEQ ID NO 53 <211> LENGTH: 24 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 53 24

85

<213> ORGANISM: Artificial Sequence

oligonucleatide

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

Human 2'-0-methyl phosphorothicate antisense

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86
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gaaggauguc uuguaaaaga acc
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<211 > LENGTH: 20
<212> TYPE: RNA
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87

88 -continued 20

<210> SEQ ID NO 60 <211> LENGTH: 24

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<212> TYPE: RNA <213> ORGANISM: Artificial Sequence

<220> FEATURE:

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<400> SEQUENCE: 60

caugacacac cuguucuuca guaa

24

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<212> TYPE: RNA <213> ORGANISM: Artificial Sequence

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24

<210> SEQ ID NO 63 <211> LENGTH: 31 <212> TYPE: RNA

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<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide

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gecaugeacu aasaaggeac ugeaagacau u

31

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<212> TYPE: RNA

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<220 > FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide

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24

ucunuaaage caguugugug aauc

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<212 TYPE: RNA

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89

90 -continued <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense 21

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<400> SEQUENCE: 66

<220> FEATURE

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guacauaegg ccaguuuuug aagac

25

<210 > SEQ ID NO 67 <211> LENGTH: 31 <212> TYPE: RNA

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cuagaucege uuuuaaaace uguuaaaaca a

31

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<400 > SEQUENCE: 68

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31

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<220 > FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide

<400> SEQUENCE: 69

cuagaucege uuuuaaaaee uguua

25

<210> SEQ ID NO 70

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<213 > ORGANISM: Artificial Sequence

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23

cogucuucug ggucacugac uua

oligonucleotide

-continued

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91

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gaucuuguuu gagugaauac agu
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94
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   guuauccage caugeuuccg uc
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  ugauaauugg uaucacuaac cugug
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  <220> FEATURE:
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95

gaaggagaag agauucuuac cuuacaaa

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2205 OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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  2223 OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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                                                                            19
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  <212> TYPE: RNA
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 aucugcauua acacccucua gaaag
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     oligonucleotide
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       <400> SEQUENCE: 88
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                                                                                                                                                                        20
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                                                                                                                                                                     20
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gucugcauce aggaacaugg guc
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100
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   <220> FEATURE:
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        oligonucleotide
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  <212> TYPE: RNA
  <213> ORGANISM: Artificial Sequence
  <220> FEATURE:
  <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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       oligonucleotide
  :400> SEQUENCE: 95
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                                                                           24
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  <211> LENGTH: 22
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  <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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      oligonucleotide
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                                                                           22
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      oligonucleotide
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acugeuggae ecauguecug aug
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cuaaguugag guauggagag u
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101

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105

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oligonucleotide

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114 -continued <210> SEQ ID NO 133 <211> LENGTH: 27 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <223 > OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense <400> SEQUENCE: 133 gucuuuauca ccauuuccac uucagac 27 <210 > SEQ ID NO 134 <211> LENGTH: 25 <212> TYPE: RNA <213 > ORGANISM: Artificial Sequence <220 > FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 134 cegucugeuu uuucuguaca aucug 25 <210> SEQ ID NO 135 <211> LENGTH: 22 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 135 uccauaucug uageugeeag ee 22 <210> SEQ ID NO 136 <211> LENGTH: 23 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 136 ccaggcaacu ucagaaucca aau 23 <210> SEQ ID NO 137 <211 > LENGTH: 30 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 137 30 uuucuguuac cugaaaagaa uuauaaugaa <210 > SEQ ID NO 138 <211> LENGTH: 25 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense

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210> SEQ ID NO 167 <2115 LENGTH: 20 <212 > TYPE: RNA <213> ORGANISM: Artificial Sequence <220> FEATURE: 2233 OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 167 aucugucaaa ucgccugcag 20 <210> SEQ ID NO 168 <211> LENGTH: 20 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 168 uuaccuugac uugcucaagc 20 <210> SEO ID NO 169 <211> LENGTH: 20 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 169 uccagguuca agugggauac 20 <210> SEQ ID NO 170 <211> LENGTH: 25 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 170 25 gcucuucugg gcuuauggga gcacu <210> SEQ ID NO 171 <211> LENGTH: 27 <212> TYPE: RNA <213> ORGANISM: Artificial Sequence <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic <220> FEATURE: Human 2'-0-methyl phosphorothicate antisense oligonucleotide <400> SEQUENCE: 171 27 accuuuauce acuggagauu ugucugc <210 > SEQ ID NO 172 <211 > LENGTH: 21 <212> TYPE: RNA <213 > ORGANISM: Artificial Sequence <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-0-methyl phosphorothicate antisense oligonucleotide

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131

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133

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137

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139

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140

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What is claimed is:

1. A method for treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation of the DMD gene that is amenable to exon 53 skipping, comprising administering to the patient an antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, 40 wherein the base sequence comprises at least 12 consecutive

bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein the antisense oligonucleotide is administered intravenously.

\* \* \* \*

# EXHIBIT 4

Neuromuscular disorders : NMD. **DUP** - General Collection W1 NE337GB v. 12, suppl. 1 Oct. 2002



### Supplement

ENMC CENTENNIAL WORKSHOP ON THERAPEUTIC POSSIBILITIES IN DUCHENNE MUSCULAR DYSTROPHY

Naarden, The Netherlands, 30 November-2 December, 2001

Guest Editor: V Dubowitz

Editor-in-Chief

### V Dubowitz UK

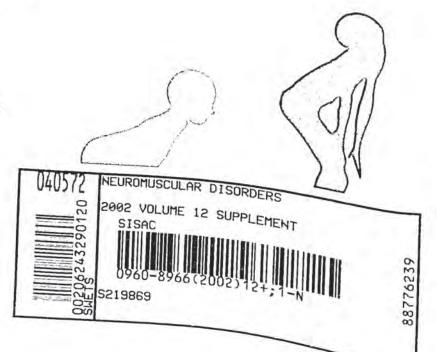
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Editor-in-Chief

V Dubowitz

Volume 12 Supplement 1 (2002)

### Therapeutic Possibilities in Duchenne Muscular Dystrophy

Proceedings of the Special Centennial International ENMC Workshop

Naarden, The Netherlands, 30 November-2 December 2001

Guest Editor:

Victor Dubowitz



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Volume 12 Suppl. 1 #. 5555 October 2002

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### Targeted exon skipping as a potential gene correction therapy for Duchenne muscular dystrophy

Annemicke Aartsma-Rus, Mattie Bremmer-Bout, Anneke A.M. Janson, Johan T. den Dunnen, Gert-Jan B. van Ommen, Judith C.T. van Deutekom\*

Department of Human Genetics, Leiden University Medical Center, Wassemarseweg 72, 2333 AL Leiden, The Netherlands

### Abstract

Duchenne muscular dystrophy is primarily caused by frame-disrupting mutations in the Duchenne muscular dystrophy gene which abort dystrophin synthesis. We have explored a gene correction therapy aimed at restoration of the reading frame in Duchenne muscular dystrophy patients. Through the binding of antisense oligoribonucleotides to exon-internal sequences in the pre-mRNA, the splicing can be manipulated in such a manner that the targeted exon is skipped and a slightly shorter, but in-frame, transcript is generated. We recently showed that antisense oligoribonucleotide-mediated skipping of exon 46 efficiently induced dystrophin synthesis in cultured muscle cells from Duchenne muscular dystrophy patients carrying an exon 45 deletion. In this study we have identified antisense oligoribonucleotides with which the skipping of 11 other Duchenne muscular dystrophy exons could be induced in cultured human muscle cells. The targeted skipping of only one particular exon may restore the reading frame in a series of patients with different mutations. Accordingly, these antisense oligoribonucleotides would allow correction of over 50% of deletions and 22% of duplications reported in the Leiden DMD-mutation Database, © 2002 Elsevier Science B.V. All rights reserved.

Keywards: Duchenne muscular dystrophy; Gene correction therapy; Antisense oligoribonucleotide; Exon skipping

### 1. Introduction

Duchenne muscular dystrophy (DMD) is predominantly caused by mutations in the DMD gene that disrupt the open reading frame of the transcript [1-3]. Consequently, the translation of the transcript into the dystrophin protein is aborted. Since dystrophin plays an important role in the muscle fiber's structure and function [1,4-7], dystrophin deficiency leads to a severe and progressive muscle degeneration and, eventually, to premature death of DMD patients.

Many gene therapy studies on DMD have focused on the gene addition strategy aiming to introduce into the patient's muscle tissue a cloned DMD coding sequence that can replace the function of the original defective DMD gene. However, the various gene delivery systems using either viral or non-viral vectors, have, notwithstanding the challenge of the large size of the coding sequence (11 kb), only been modestly capable of transducing sufficient muscle fibers for long time-periods [8]. Therefore, other strategies, such as pharmacological therapy or gene correction, have recently gained increasing attention. We have been studying

the feasibility of targeted exon skipping to modulate the splicing of the DMD gene in such a manner that the translational open reading frame is restored in muscle cells from DMD patients. Theoretically, this may be therapeutically applicable to the majority of DMD mutations. In case of deletions, exon skipping would result in slightly shorter, but in-frame, transcripts, similar to those found in the corresponding Becker muscular dystrophy (BMD) patients, having milder phenotypes and significantly longer life expectancies when compared to DMD patients [2,3]. Exon skipping in DMD patients carrying single exon duplications should be even more effective, because of the double target dosage and the generation of a true wild-type dystrophin as the product resulting from skipping one of the two exons. Finally, point mutations in any of the 'in-frame' exons in the DMD gene may also be bypassed by single exon skipping, inducing a small in-frame exon deletion which is often associated with a Becker-like dystrophin protein.

The mechanism of exon skipping is based upon antisense oligoribonucleotides (AONs), small synthetic RNA molecules that can bind to specific sequences within the DMD pre-mRNA [9-12]. Several studies have shown the feasibility of AON-mediated exon skipping by targeting sequences involved in the splicing process. In muscle cells of the mdx mouse, a DMD mouse model carrying a nonsense mutation

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in exon 23 [13]. AONs directed to the 3' or 5' splice sites induced exon 23 skipping and so restored the reading frame to therapeutic levels [14-16]. However, these splice sitespecific AONs also caused less predictable skipping of additional, adjacent exons. As this may be explained by nonspecific interference with the splicing machinery, splice sites may be less optimal targets for AON-mediated exon skipping. In another study [17,18], the skipping of exon 19 was specifically induced in human muscle cells, using AONs directed to an exon-internal sequence that was considered to be a splicing enhancer sequence [19,20]. Similarly, we showed specific exon 46 skipping in mouse and human muscle cells using exon-internal AONs. These AONs targeted a sequence in exon 46 with a relatively high purine-content, that was predicted to have an open, accessible, secondary RNA structure, and, by resembling an exon recognition site [19,20], was suggested to be involved in the splicing process. Following transfection of these AONs into muscle cells from two unrelated Duchenne patients affected by an exon 45 deletion, the interrupted open reading frame was corrected and the synthesis of a slightly shorter dystrophin induced in at least 75% of treated muscle cells [21]. Based on the fact that there are more mildly affected Becker dystrophy patients with a deletion of both exons 45 and 46, this shorter protein is expected to be largely functional.

In this follow-up study, we further tested the in vitro feasibility of exon skipping using AONs directed to exoninternal sequences. The skipping of a single exon from a normal mature mRNA generates either an out-of-frame or an in-frame transcript. We designed and tested a series of AONs directed to eight out-of-frame exons (exons 2, 43, 44, 45, 46, 50, 51 and 53) and seven in-frame exons (exons 29, 40, 41, 42, 47, 48, and 49). Skipping of these exons would correct the majority of the most frequently occurring Duchenne deletions (>60%) and duplications (>22%), and various DMD-causing point mutations. The efficacy of the AONs and, hence, the 'skipability' of the targeted exons was analyzed in cultured human myotubes.

### 2. Materials and methods

### 2.1. AONs and primers

A series of AONs (two per exon, see Table 1) was designed to bind to exon-internal target sequences showing a relatively high purine-content and, preferably, an open secondary pre-mRNA structure (at 37 °C), as predicted by the RNA mfold version 3.1 server [22]. The AONs varied in length between 15 and 24 bp, with G/C contents between 26 and 67%. They were synthesized with the following chemical modifications; a 5'-fluorescein group (6-FAM), a full-length phosphorothioate backbone and 2'-O-methyl modified ribose molecules (Eurogentec, Belgium). The primers used for reverse transcription–polymerase chain reaction (RT–PCR) analysis (Table 2) were synthesized by Eurogen-

tee (Belgium) or by Isogen Bioscience BV (The Netherlands).

### 2.2. In vitro experiments

Primary human myoblasts were isolated from a muscle biopsy from a non-affected individual (KM108) by enzymatic dissociation. Briefly, the tissue was homogenized in a solution containing 5 mg/ml collagenase type VIII (Sigma), 5 mg/ml bovine albumin fraction V (Sigma), 1% trypsin (Gibco BRL) in PBS (Gibco BRL). Following serial incubation steps of 15 min at 37 °C, suspensions containing the dissociated cells were added to, and pooled in, an equal volume of proliferation medium (Nut.Mix F-10 (HAM) with GlutaMax-1, Gibco BRL) supplemented with 20% fetal bovine serum (Gibco BRL) and 1% penicillin/streptomycin solution (Gibco BRL). After centrifugation, the cells were plated and further cultured in proliferation medium, using flasks that were pre-coated with purified bovine dermal collagen (Vitrogen 100; Cohesion). The myogenic cell content of the culture, as determined by the percentage of desmin-positive cells in an immunohistochemical assay, was improved to 58% by repetitive preplating [23]. Myotubes were obtained from confluent myoblast cultures following 7-14 days of incubation in low-serum medium (DMEM (Gibco BRL), supplemented with 2% GlutaMax-1, 1% glucose, 2% fetal bovine serum and 1% penicillin/ streptomycin solution). For transfection of the myotube cultures, we used polyethylenimine (PEI; ExGen 500) according to the manufacturer's instructions (MBI Fermentas). The cultures were transfected for 3 h in low-serum medium with 1 µM of each AON linked to PEI at a ratioequivalent of 3.5.

### 2.3. RNA isolation and RT-PCR analysis

At 24 h post-transfection, total RNA was isolated from the myotube cultures using RNAzol B according to the manufacturer's instructions (Campro Scientific, The Netherlands). One microgram of RNA was then used for RT–PCR analysis using *C. therm* polymerase (Roche Diagnostics) in a 20-µl reaction at 60 °C for 30 min, primed with different DMD gene-specific reverse (RT) primers (Table 2). Primary PCRs were carried out with outer primer sets (see Table 2), for 20 cycles of 94 °C (40 s), 60 °C (40 s), and 72 °C (90 s). One microliter of this reaction was then reamplified in nested PCRs using the appropriate primer combinations (Table 2) for 32 cycles of 94 °C (40 s), 60 °C (40 s), and 72 °C (60 s). PCR products were analyzed on 1.5 or 2% agarose gels.

### 2.4. Sequence analysis

RT-PCR products were isolated from agarose gels using the QIAquick Gel Extraction kit (Qiagen). Direct DNA sequencing was carried out by the Leiden Genome Technology Center (LGTC) using the BigDye Terminator Cycle

Table 1

Characteristics of the AONs used to study the targeted skipping of 15 different DMD exons<sup>a</sup>

| Name                  | Antisense sequence (5'-3')               | Length (bp) | G/C% | U/C% | Exon skip | Transcript |
|-----------------------|--|-------------|------|------|-----------|------------|
| h2AON 1               | cccauuuugugaauguuuucuuuu                 | 24          | 29   | 7.5  | +         | OF         |
| h2AON 2               | uugugcauuuacccauuuugug                   | 22          | 36   | 68   | -         | OI;        |
| 129AON 1              | uauccucugaaugucgcauc                     | 20          | 4.5  | 65   | +         | IF         |
| h29AON 2              | gguuauccucugaaugucgc                     | 20          | 50   | 60   | +         | 1F         |
| h40AON I              | gagccuuuuuucuucuuug                      | 19          | 37   | 79   | +         | IF         |
| 640AON 2              | uccuuucgucucugggcuc                      | 19          | 58   | 79   | +         | IE.        |
| h41AON I              | cuccucuucuucuucuga                       | 19          | 47   | 95   | +         | 1F         |
| h41AON 2              | cuucgaaacugagcaaauuu                     | 20          | 35   | 50   | +         | 1k         |
| h42AON I              | cuugugagacaugagug                        | 17          | 47   | 41   | +         | 1F         |
| h42AON 2              | cagagacuccucuugcuu                       | 18          | 50   | 67   | +         | 117        |
| h43AON I              | ugcugcugcuucuugcu                        | 18          | 50   | 78   |           | OF         |
| h43AON 2              | uuguuaacuuuuucccauu                      | 19          | 26   | 79   | +         | OF         |
| h44AON 1              | cgccgccauuucucaacag                      | 19          | 58   | 6.3  | +         | OF         |
| h44AON 2              | uuuguauuuagcauguuccc                     | 20          | 35   | 70   | +         | OF         |
| h45ΛΟΝ 1              | geugaauuauuucuuccc                       | 19          | 42   | 74   | ~         | OF         |
| h45AON 2              | uuuuucugucugacagcug                      | 19          | 42   | 68   | -         | OF         |
| h46AON 4h             | cugcuuccuccaacc                          | 15          | 60   | 80   | +         | OF         |
| h46AON 8 <sup>b</sup> | gcuuuucuuuuaguugcugc                     | 20          | 40   | 75   | +         | OF         |
| h47ΛΟΝ 1              | ucuugcucuucugggcuu                       | 18          | 50   | 78   | -8        | II.        |
| h47AON 2              | cuugagcuuauuuucaaguuu                    | 21          | 29   | 67   |           | II.        |
| h48AON I              | uuueueeuuguuueue                         | 16          | 38   | 94   | -         | 11:        |
| h48AON 2              | ccauaaauuuccaacugauuc                    | 21          | 33   | 62   | -         | 1F         |
| h49AON I              | cuuccacauccgguuguuu                      | 19          | 47   | 7.4  | +         | IF.        |
| h49AON 2              | guggcugguuuuuccuugu                      | 19          | 47   | 68   | +         | 117        |
| h50AON I              | cucagagcucagaucuu                        | 17          | 47   | 59   | +         | OF         |
| h50AON 2              | ggcügcüüügcccuc                          | 15          | 67   | 73   | =         | OF         |
| h51AON I              | ucaaggaagauggcauuucu                     | 20          | 40   | 45   | +         | OF         |
| h51AON 2              | ccucugugauuuuauaacuugau                  | 23          | 30   | 65   | +         | OI:        |
| h53AON I              |  | 18          | 61   | 72   | +         | OL         |
| h53ΛON 2              | cuguugecucegguucug<br>uuggeucuggecuguceu | 18          | 61   | 72   | -         | OF         |

<sup>\*</sup> Two ΛONs were tested per exon. Their different lengths and G/C contents (%) did not correlate to their effectivity in exon skipping (+, induced skipping, -, no skipping). The AONs were directed to purine (A/G) -rich sequences as indicated by their (antisense) U/C content (%). Skipping of the target exons resulted in either an in-frame (IF) or an out-of-frame (OF) transcript.

h van Deutekom et al., 2001 [21].

Table 2 Primer sets used for the RT-PCR analyses to detect the skipping of the targeted exons\*

| Target exon | RT-primer | Primary PCR<br>primer set | Nested PCR<br>primer set |  |
|-------------|-----------|---------------------------|--------------------------|--|
| 2           | h4r       | hIfI-h4r                  | h1f2-h3c                 |  |
| 2 2         | h9r       | h1f1-h9r                  | h1f2-h8r                 |  |
| 29          | h31r      | h25f-h31r                 | h26f-h30r                |  |
| 40          | h44r      | h38f-h44r                 | h39f-h43r                |  |
| 41          | h44r      | h38f-h44r                 | h39f-h43r                |  |
| 42          | h-1-1r    | h38f-h44r                 | h39f-h43r                |  |
| 43          | h-47r     | h41f-h47r                 | h42f-h46r                |  |
| 44          | h47r      | h416-h47r                 | h42f-h46r                |  |
| 45          | 11471     | h41f-h47r                 | h42f-h46r                |  |
| 46          | h48r      | h44f-h48r                 | h45f-h47r                |  |
| 47          | h52r      | h44f-h52r                 | h46f-h51r                |  |
| 48          | b52r      | h44f-h52r                 | h46f-h51r                |  |
| 49          | h52r      | h44f-h52r                 | h46f-h51r                |  |
| 50          | h52r      | h44f-h52r                 | h46f-h51r                |  |
| 51          | h53r      | h47f-h53r                 | h49f-h52r                |  |
| 53          | h55r      | h50f-h55r                 | h51f-h54r                |  |

A Primer sequences are available upon request.

Sequencing Ready Reaction kit (PE Applied Biosystems), and analyzed on an ABI 3700 Sequencer (PE Applied Biosystems).

#### 3. Results

### 3.1. In vitro exon skipping

AONs were empirically analyzed for the induction of exon skipping following transfection into human control myotube cultures, using the cationic polymer polyethylenimine (PEI). As determined by the nuclear uptake of the fluorescent AONs, average transfection efficiencies of 60–80% were obtained. At 24 h post-transfection, transcripts were analyzed by RT-PCR using different primer combinations encompassing the targeted exons (Table 2). Of the 30 AONs tested, a total of 20 (67%) reproducibly generated shorter transcript fragments with sizes corresponding to the specific skipping of the targeted exons (Fig. 1 and Table 1). In fact, as confirmed by sequence analysis of the shorter transcripts (data not shown), we could induce the

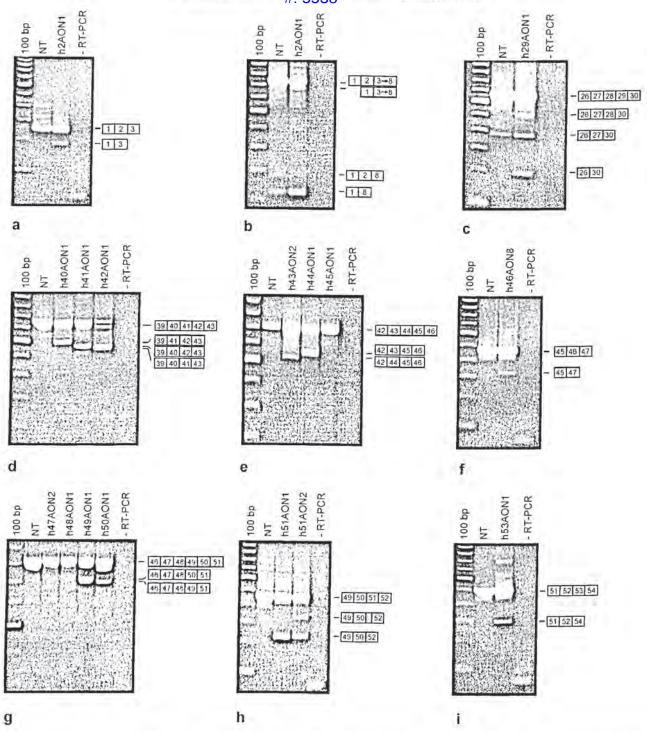


Fig. 1. RT=PCR analysis of human dystrophin mRNA in the regions encompassing the exons Jargeted for skipping. Shorter, novel transcript fragments were observed following transfection with the different AONs when compared to non-transfected myotube cultures (NT). Sequence analysis (not shown) confirmed the skipping of the targeted exons, as indicated by the labels adjacent to the images. Alternatively spliced products, detected in the regions around exon 2 (b), exon 29 (c), and exon 51 (b), were sequenced and found to be derived from either co-skipping of adjacent exons or usage of a cryptic splice site. No aspecific (RT=) PCR products were obtained. In some analyses, additional fragments, slightly shorter than the wild-type products, were present. This was due to heteroduplex formation.

specific skipping of 12 out of the 15 exons targeted (five out of the seven in-frame exons, and seven out of the eight out-of-frame exons). No skipping of exons 45, 47 and 48 was detected (Fig. 1e,g).

In the specific transcript regions that were screened in these experiments, we observed in the non-transfected control myotubes alternative splicing patterns around exons 2 and 29 (Fig. 1b,c). The alternative products were sequenced and found to be due to the skipping of exons 2–7 (in-frame), exons 3–7 (out-of-frame), exons 28–29 (in-frame), and exons 27–29 (in-frame). This genuinely occurring exon skipping was also detected previously in human

skeletal muscle [24,25]. Remarkably, the level of the alternative splicing was significantly enhanced by the AON-treatment of the transfected myotube cultures. Noteworthy also is the observation that h2AON1 not only induced exon 2 skipping in the normal transcript, but also in one of the alternative transcripts consisting of exons 1 and 2 spliced to exon 8 (Fig. 1b).

The majority of AONs induced the precise skipping of the targeted exons, using the original splice sites of the adjacent exons. However, in response to h51AON2, an in-frame cryptic splice site was used in exon 51 (Fig. 1h). The level of this alternatively spliced product was variable in serial transfection experiments. Finally, in some of the transfection experiments, additional aberrant splicing fragments were detected due to the co-skipping of adjacent exons. Their incidence, however, was inconsistent, and at very low levels.

### 4. Discussion

In the field of DMD gene therapy, gene correction by antisense-induced exon skipping is gaining attention as a novel and promising tool in development. The feasibility and therapeutic potential of this strategy has been demonstrated both in human muscle cells for exon 19 [17] and exon 46 [21], and in mouse muscle cells for exon 23 [14–16]. The strategy is based upon antisense oligoribonucleotides, generally considered to be small and relatively safe therapeutic reagents, which bind to target sequences in the pre-mRNA and so induce exon skipping. Whilst this

suggests a mutation-, i.e. a patient-, specific therapy, an important intrinsic advantage over gene addition is the simultaneous correction of most or all affected dystrophin isoforms, thus enabling the maintenance of the original tissue-specific gene regulation. Moreover, an assessment of the mutation spectrum shows that the skipping of one particular exon would theoretically be therapeutic to a series of different mutations. For instance, the skipping of exon 51 would restore the reading frame in patients carrying a deletion of either exons 45-50, 47-50, 48-50, 49-50, 50, 52, or 52-63. In fact, skipping of the 12 different exons that were successfully targeted in this study, would, in total, correct more than 50% of the deletions and 22% of the duplications reported in the Leiden DMD-mutation Database (Table 3). Therefore, the method, once established, would be widely applicable. Another promising aspect is the efficiency of the skipping strategy. In a previous study we showed that by inducing exon 46 skipping in muscle cell cultures from DMD patients affected by an exon 45 deletion, an inframe transcript (lacking both exons 45 and 46) was generated at estimated levels of 15% of total mRNA, which restored dystrophin synthesis to near normal levels in over 75% of myotubes [21]. These results, together with those from mini-DMD gene addition studies in mice showing that only one third of normal dystrophin expression already ameliorates the dystrophic phenotype [26], underline the potential of the exon skipping strategy.

To test the realistic applicability of the strategy to other exons and hence other mutations, we have targeted here 15 different exons that were selected on the basis of being located in the deletion hot spot region, thereby theoretically

Table 3
Overview and frequency of the DMD-causing mutations in the Leiden DMD (LDMD) Database, theoretically correctable by skipping one of the 12 exons successfully targeted in this study

| Skipable exon | Therapeutic for DMD-mutations:  |                                    |                      |  |  |  |  |
|---------------|---|------------------------------------|----------------------|--|--|--|--|
|               | Deletions (exons)   | % of deletions in<br>LDMD Database | Duplications (exons) | % of duplications<br>in LDMD<br>Database | No. of nonsense<br>mutations in<br>LDMD Database |  |  |
| 2             | 3-7, 3-19, 3-21   | 2.9                                | 2                    | 9.0                                      | ż  |  |  |
| 29            |   |                                    |                      |  | 1  |  |  |
| 40            |   |                                    |                      |  | 7  |  |  |
| 41            |   |                                    |                      |  | 0  |  |  |
| 12            |   |                                    | 1.00                 | 3,0                                      |  |  |  |
| 13            | 44, 44-47, 44-49, 44-51   | 3.7                                | 43                   |  |  |  |  |
| 44            | 5-43, 14-43, 19-43, 30-<br>43, 35-43, 36-43, 40-43,<br>42-43, 45, 45-54 | 7.8                                | 44                   | 3,0                                      |  |  |  |
| 46            | 21-45, 45, 47-54, 47-56   | 5.6                                |                      |  | 1  |  |  |
| 49            |   |                                    |                      | 2.0                                      |  |  |  |
| 50            | 51, 51-53, 51-55  | 5.2                                | 50                   | 3,0                                      |  |  |  |
| 51            | 45-50, 47-50, 48-50,<br>49-50, 50, 52, 52-63                            | 17.5                               | 51                   | 1.5                                      |  |  |  |
| 53            | 10-52, 45-52, 46-52,<br>47-52, 48-52, 49-52,<br>50-52, 52               | 7.5                                |                      |  |  |  |  |

applicable to the majority of DMD deletions, and on being either in-frame (exons 29, 40, 41, 42, 47, 48, and 49) or outof-frame (exons 2, 43, 44, 45, 46, 50, 51 and 53). The 30 AONs that were designed for these experiments differed in length and in G/C content. They were principally directed to relatively purine-rich sequences, which in most cases were predicted to have an open secondary RNA structure at 37 °C. Using these AONs we were able to induce the skipping of 12 out of the 15 targeted exons. There was no significant difference in 'skipability' between in-frame exons or out-offrame exons, or between exons with weak (mostly in-frame) or strong splice-site consensus sequence values [27]. It has been suggested that exons with weak splice site consensus values may require additional signals, such as secondary or tertiary structural motifs that interact with the splicing machinery, to ensure accurate splicing. Based on our results, we hypothesize that the binding of the AON to the exon disturbs the local folding of the pre-mRNA to such an extent that the spliceosomal complex is sterically hindered, or no longer recognizes the exon for inclusion, and consequently skips it during the splicing process. This is supported by the fact that in some transfection experiments, in response to the different AON treatments, we observed the enhancement of naturally occurring or newly induced alternative splicing patterns. The alternative splicing was found to be due to the co-skipping of exons adjacent to the targeted exon. which can be explained by their close location within the same local pre-mRNA folding pattern. Although alternative splicing patterns in response to AON treatment is an unintended side effect, it is of minor relevance for the therapeutic applicability of targeted exon skipping. If the resulting alternative transcripts are out-of-frame, they will, as with the original out-of-frame transcript in the DMD patients, be non-functional and probably less stable due to nonsensemediated mRNA decay. However, any resulting in-frame product, either derived from the precise skipping of the targeted exon, the unintended co-skipping of (an) additional exon(s), or the usage of cryptic splice sites (as observed in exon 51), will induce the synthesis of a shorter, but largely functional, dystrophin protein, and thus be beneficial for the DMD patient.

Of the 30 AONs tested, as many as 20 induced specific exon skipping. There was no significant correlation between the length or sequence content of the AON and its effectiveness (see Table 1). We hypothesize that in most cases the mere accessibility of the targeted RNA region, and thus the capability of the AONs to bind, determines their efficacy. The fact that with the AONs tested so far, we have not been able to induce the skipping of exons 45, 47 and 48 would, in this model, be explained by a less accessible configuration of these exons within the secondary structure of the pre-mRNA. To predict the secondary structure of the targeted pre-mRNA regions, we have used the RNA mfold version 3.1 server [22]. Although this analysis hints at the most favorable local structure which may help in the design of AONs, it is not capable of predicting the

overall complex structure of the entire DMD pre-mRNA. We therefore have no insight into the actual position of the targeted sequence within the completely folded RNA structure. Its accessibility, and thus the effectivity of any designed AON, will therefore still have to be tested empirically in the cells, as was done in this study. We are currently analyzing the therapeutic applicability of the effective AONs in cultured muscle cells from DMD patients affected by the different deletions, duplications, and nonsense mutations described in Table 3.

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